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Statistics

INTERPRETATION AND ESTIMATION OF CONDITIONAL POWER IN INTERIM ANALYSES OF CLINICAL TRIALS: OFTEN IGNORED IN DECISION MAKING PROCESS

S. Marimuthu	M.Sc., Department of Biostatistics, Christian Medical College, Vellore, Tamil Nadu, India.
Mani Thenmozhi	Ph.D., Department of Biostatistics, Christian Medical College, Vellore, Tamil Nadu, India.
Melvin Joy	M.Sc., TRCI, Faculty of Medical Sciences, Newcastle University, UK.
Malavika Babu	M.Sc., Centre for Trials Research, College of Biomedical and Life Science, Cardiff University.
Thambu David Sudarsanam	MD Dip.NB., Department of Medicine, and Clinical Epidemiology Unit, Christian Medical College, Vellore, Tamil Nadu, India.
L. Jeyaseelan*	Ph.D., Department of Basic Sciences, MBR University of Medicine and Health Sciences, Dubai, UAE. *Corresponding Author

ABSTRACT In group sequential trials, the interim results are more promising in the early termination of a trial either for efficacy or futility of the trial. This reduces the cost and time implications. Moreover, interim analyses play a key role to tackle the problem that arises due to adverse effects. In concern with the early stopping of trials, there are numerous stopping methods among them the Conditional power (CP) approach is best recommended. The CP approach provides the probability of getting significant results at the end of the study given the data observed so far. There are very few Indian studies that had incorporated the concept of CP and made decisions based on the results. This study popularises the CP approach detailing computing and its interpretation and is thereby facilitating clinical researchers to use this approach effectively. We have used real-time and hypothetical examples and illustrated the concept of CP under trend, CP under null, and CP under design. We suggest stopping the study for efficacy when the CP under null is greater than 80% and stopping the study for futility when CP under trend is less than 30%.

KEYWORDS : Clinical trial; Conditional Power; Efficacy and Futility; Group sequential trial; Interim analysis;

Background:

In group sequential trials, the interim results are more promising in early stopping of a trial either for efficacy or futility (1). This reduces the cost and time implications. The group sequential trial is planned when the study duration is for more than a year and the data is accumulated over a period of time. During the trial period, the investigators need to monitor the data for adverse events and the results with the view to taking action such as early termination or adapt changes in the design such as changing the sample size, inclusion and exclusion criteria etc. The ethical reason to monitor results is to ensure that individuals are not exposed to unsafe, inferior or ineffective treatment regimens. If no significant difference between two interventions is observed, then there is an ethical imperative to terminate the trial at the earliest so that resources can be allocated to study for the next promising intervention waiting to be tested. Moreover, the interim results may sometimes reveal the presence of problems which can be remedied before too much expense is incurred (2).

However, if the study design is group sequential trial, then number interim analyses and the stopping rules have to be planned. Conservatively Pocock has recommended five interim analyses and the p value <0.01 to stop the study (2). On the other hand, O Brien Fleming *et al.* have recommended different p values for each interim analysis. That is, p value is kept very low at early interim analyses and gets relaxed as the number of interim analyses increased or an accumulated data size increased (3,4). Based on a priori stopping rule, if the difference is significant then the investigators decide to stop the study. At the moment of taking decision, following questions need to be asked: 1. Whether the obtained current difference is likely to continue in the future as well if the study continued. If so, then what is the power? Next, what is the probability of getting significant result at the end of the study when there is no difference in future? That is, the current difference is significant and even if the future interim data shows no difference, will the pooled difference provide the significant result?

The power in a study is the probability of rejecting the null hypothesis when it is false. That is, if the power is 90% which means that if the study gets repeated for 100 times, 90 times we would reject the null hypothesis when it is false. The calculated power for the given data is less than 80%, one of the reasons could be that the study does not have enough sample size to reject the null hypothesis. In the same manner, conditional power (CP) at the interim analysis is the probability of rejecting the null hypothesis given the observed data so far and the specific assumption about the treatment effect (difference) in the rest of the study.

Let us consider a hypothetical example of two anti cancer drugs trial A and B, assuming a 50% reduction in the response rate of drug B as compared to A. The estimated sample size was about 70 in each arm. As the recruitment of subjects takes a longer time, it is reasonable to plan five interim analyses with about 14 patients per arm. Suppose in the third interim analysis, there will be 42 patients and their outcomes will be available in each arm. For instance, if there is 14% difference between the two arms, which favors the new treatment (A). Shall we take a decision to stop the study? If yes, is it for benefit or futile? Conditional power (CP) analysis will provide evidence to answer these questions and facilitate decision making either to continue or stop the study early.

Walter *et al.* (5) had studied 52 eligible trials, covering many clinical areas, of which 75% have planned one interim analysis as a priori. They also reported that the majority of trials did not pre-define stopping criteria, and a variety of reasons were given for stopping. However, it is unclear whether the studies carried out in developing countries have reported the decision making processes and the reasons for stopping the trial. We have searched the key word "Interim analysis AND India" in Pubmed search engine and found six such articles. Of them, only one study used the concept of CP and presented the data. Murki *et al.* (6) stopped the trail early for efficacy. Swaminathan *et al.* (7) stopped the trial for futility based on O'Brien-Fleming Boundary. Neogi *et al.* (8) stopped the trial after the first interim results based on CP analysis. Sur *et al.* (9) and Shah *et al.* (10) presented the interim analysis results but they did not conduct CP analysis. Over all, few articles had incorporated interim analyses in the design and only one study has used CP concept for decision making.

There are many reasons why the CP is not done in group sequential trials, which are analytical, administrative and subjective reasons. Mostly, the reasons are unanticipated toxicity, unlikely possibility of a positive results, inadequate recruitment, poor compliance, poor

quality of data, loss of financing, results from other trials and changes in treatment etc. These reasons could override the estimation of CP given the data so far. However, this paper aims to disseminate the conditional power analysis concept, computing details, interpretation to facilitate researchers to use these methods effectively.

Methods:
Conditional power is the probability of getting significant results at the end of the study given the observed data so far and a specific assumption about the pattern of the data to be observed in the rest of the trial, such as design effect, or the effect estimated from the interim data (trend), or under the null hypothesis (11,12).

CP under Trend (CP_{CT}):
One may rely more directly on the interim data, and assume that the current observed value of treatment effect will continue in the future data (data to be observed between the interim and final analyses) and it is called CP under trend (CP_{CT}).

CP under Null (CP_{Null}):
Assume a pessimistic scenario that is no difference between two interventions in the future interim analysis and it is called CP under null (CP_{Null}).

CP under Deign (CP_D):
The researchers usually assume the treatment effect in the planning stage to calculate sample size based on their experience and literature reviews. One may assume that the difference between the two interventions in the future interim analysis would be what was planned in the beginning then it is called CP under design (CP_D).

The formula for CP under Trend, Null, and Design were given in Appendix I. Also, the CP calculation for two proportions comparison is given in Appendix II. Besides, we have developed an online calculator using R package "shiny", to calculate the CP for comparing two means and proportions, the link: *https://bio-statistics.shinyapps.io/CP-Dash/*

Stopping Criteria:
Based on the literature review and from our experience, we suggest the following stopping criteria to stop the study early for benefit or futility. If CP_{CT} is less than 30%, we recommend stopping the study for futility. If the CP_{Null} is greater than or equal to 80%, we advised stopping the study for benefit. The detailed discussion of the stopping criteria is given in the discussion.

Data:
To illustrate the conditional power concept, we have used a hypothetical data and two real time studies which are described below:

Hypothetical Data:
We considered a hypothetical data with two anti cancer drugs A and B, assuming a 50% reduction in the response rate of drug B as compared to drug A. The response rate among patients who were treated with drug A was 50%. The required sample size to estimate 50% reduction in drug B, with 85% power, 5% alpha and two sided test is about 70 in each arm. Therefore, it is reasonable to plan five interim analyses with equal number of subjects for each interim analysis, 14 patients each per arm. The interim results were presented in Figure 1.

Interim Analyses	Arm A	Arm B	Mean Difference	Standard Error	P value
1	9/14	3/14	0.43	0.17	0.022
2	18/28	10/28	0.28	0.13	0.033
3	23/42	17/42	0.14	0.11	0.189
4	26/56	22/56	0.07	0.09	0.445
5	28/70	25/70	0.04	0.08	0.601

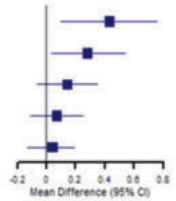

Figure1: Interim Analyses Results Of Hypothetical Data

Early Stopping For Futility: Study1
Boggs *et al*. (13) investigated whether maintenance temozolomide (TMZ) after definitive therapy for locally advanced Non-Small-Cell Lung Cancer (NSCLC) decreases the incidence of brain metastasis (BM). This study was designed to test whether the incidence of BM would decline from a predicted 40% in the observation arm to 15% in the TMZ arm. A sample size of 100 patients (50 per arm) was determined that would estimate with 90% certainty, a clinically important treatment difference at a 1-sided significance level of 5%. The eligible patients were randomized to observation or TMZ (75 mg/m2 for 21 consecutive days followed by a 7-day rest for up to 6 cycles or progression). The primary end point was incidence of radio graphically diagnosed BM within 12 months from day 1 of first-line chemotherapy. The study was stopped early based on futility analysis; 45 of 53 enrolled patients were evaluable from an original target of 100. No statistically significant difference was noted in the incidence of BM at 1 year in the TMZ (18%) and observation arms (18% vs. 13%; p=0.69).

Early Stopping For Efficacy: Study2
Papanikolaou *et al*. (14) designed a prospective, randomized controlled trial to determine the differences in the rates of pregnancy and delivery between women undergoing transfer of a single cleavage-stage (day 3) embryo(Arm B) and those undergoing transfer of a single blastocyst-stage (day 5) embryo(Arm A). A sample size of 351 patients in each arm would provide a statistical power of 80% to detect an absolute difference of 10% in the pregnancy rate between the groups (given rates of 20 and 30 percent) at an alpha level of 5% with two-sided test. At the first interim analysis, there were 351 infertile women (under 36 years) randomly assigned to undergo transfer of either arm B (176 patients) or arm A (175 patients). The study was terminated early after a pre-specified interim analysis (which included 50% of the planned number of patients) which indicated a higher rate of pregnancy among women undergoing transfer of arm A. The rate of delivery was also significantly higher in arm A than arm B (33.1% vs. 21.6%; p= 0.02).

RESULTS:
Hypothetical Data:
Forest plot represents the summary statistics of the hypothetical data (figure1). In the initial stage, the difference between the two arms was statistically significant at 5% level of alpha, but later on it was not. The CP statistics for hypothetical data were provided in table1.

Table1: Conditional Power Results Of Hypothetical Data

Interim analysis	*Observed Proportion in A (p1)*	*Observed Proportion in B (p2)*	*OBF stopping boundary (Z value)*	*OBF Stopping P value*	*Difference (95% CI)*	*t*	Z_t	*P value*	*CP Null (%)*	*CP trend (%)*	*CP design (%)*
1	09/14 (0.64)	03/14 (0.21)	±4.87	1.077 7E-06	0.43 (0.10, 0.76)	0.2	2.29	0.022	14.78	99.97	94.82
2	18/28 (0.64)	10/28 (0.36)	±3.36	0.000 787	0.28 (0.03, 0.54)	0.4	2.14	0.033	21.64	96.68	93.41
3	23/42 (0.55)	17/42 (0.41)	±2.68	0.006 828	0.14 (-0.07, 0.35)	0.6	1.31	0.189	6.76	33.60	64.77
4	26/56 (0.46)	22/56 (0.39)	±2.29	0.016 807	0.07 (-0.11, 0.25)	0.8	0.76	0.445	0.21	0.67	6.44
5	28/70 (0.40)	25/70 (0.36)	±2.03	0.025 576	0.04 (-0.13, 0.19)	1	0.52	0.601			

Note: OBF- O'Brien Fleming; CI – Confidence Interval; t- Information fraction; CP – Conditional Power

Interim-1:
In the first interim analysis, the difference between two arms was 43% (p=0.02). The CP_{CT} was about 100%, which means that if the same trend exists in the remaining subjects of the study, the probability of getting significant result would be about 100%. The CP_{Null} was 14.78%, which means that when there is no difference in the remaining subjects, the probability of getting significant result would be about 15%. Though the CP_{CT} is 100% as the CP_{Null} less than 80% we would suggest continuing the study.

Interim-2:
In the second interim analysis, the difference was 28% (p=0.03). The CP_{CT} was about 97%. The CP_{Null} was about 22%. As the CP_{Null} was less than 80%, we recommend to continuing the study despite the CP_{CT} was about 97%.

Interim-3:
In the third interim, the difference was 14% (p=0.19). The CP_{Null} was about 7%, the CP_{CT} was about 34%. As the CP_{Null} was less than 80% and CP_{CT} was greater than 30%, we recommend continuing the study.

Interim-4:
In the fourth interim, the difference was decreased to 7% (p=0.45). The CP_{Null} was 0.21%. The CP_{CT} was about 1%. As the CP_{CT} was less than 30%, we suggest stopping the study for futility and conclude that there is no statistically significant difference between the response rates between two arms.

Table2 indicates the planning and interim parameters and CP result for two studies. Based on the CP analysis, we suggested stopping the study conducted by Boggs *et al*. (13) for futility and continue the study by Papanikolaou *et al*. (14) due to lack of power.

Table2: Conditional Power Results Of Real Time Data

Study	Planning Parameters					Interim Parameters						Conditional Power		
	N1	N2	P1 %	P2 %	P1-P2 (%)	Proportion in A (p1)	Proportion in B (p2)	Difference (95% CI)	t	Z_t	P value	Null (%)	Trend (%)	Design (%)
Boggs et al.	50	50	40	15	25	4/22 (0.18)	3/22 (0.13)	0.05 (-0.15, 0.25)	0.52	0.498	0.309	3.18	8.42	70.45
Papanikolaou et al.	351	351			10	58/175 (0.33)	38/176 (0.22)	0.115 (0.02, 0.20)	0.5	2.31	0.021	32.13	96.74	94.89

Note: CI – Confidence Interval; t - Information fraction

Boggs *et al.* Study1: In the interim analysis, the difference was 0.05 (p=0.309). The CP_{CT} was 8.42%, suggesting that if the same trend exists in the remaining study, the probability of getting significant result would be about 8%. Similarly, the CP_{Null} was about 3% which means that in the absence of difference in the remaining subjects, the probability of getting significant result would be about 3%. Likewise, the CP_D was about 70% suggesting that the probability of getting significant results at the end of the study would be about 70%, when the design effect exists in the remaining study. Even if the design effect exists in the remaining study, it would not have enough power to show significant results, as minimum expected power is 80%. Therefore, we would suggest stopping the study for futility.

Papanikolaou *et al.* Study2: In the interim analysis, the difference was 0.115 (p=0.021). The CP_{CT} was about 97% which means that if the same difference exists in the remaining subjects of the study, the probability of getting significant result would be about 97%. The CP_{Null} was about 32% which means that if there is no difference in the remaining subjects, the probability of getting significant result would be about 32%. As the CP_{Null} was less than 80%, we would recommend continuing the study despite the CP_{CT} was about 97%.

DISCUSSION:

In group sequential trials, evidence-based stopping criteria are incorporated to minimize patient exposure to ineffective and potentially toxic experimental treatments. It indicates that if the treatment is futile or overwhelming benefit, then the trial should be stopped early. Many studies have discussed about the early stopping of trials for futility (15–17). However, the researchers are not aware of use of CP in the group sequential trials. Therefore, this study presents the CP calculation and interpretation for the entire scenario using a hypothetical data. This illustrates how the difference across the arms and CP estimates change as study progress. However, this circumstance is very rare in real time.

How The Stopping Rules Were Reported In The Previous Studies?

Walter *et al*. (5) mentioned that the reporting of the stopping rule or decision-making processes were often missing or incomplete. They also reported their concerns about the possible absence of planning of interim analysis in advance that had occurred at a later stage of studies. There was often no pre-specification for the number of planned interim analyses and the time of interim analysis. Although many trials claimed futility as the basis for stopping a trial, not much detail have been provided about the specific criteria followed for futility analysis. Many studies made general or vague allusions to the concept of futility, but without detailed analysis of the data.

Stopping For Benefit:

Usually, the researchers would expect 80% power to conclude that a new treatment is better than a standard treatment. Therefore, one can stop the study for benefit if is greater than 80% with the following condition, the CP is overwhelming even under a pessimistic assumption. It means that we got enough evidence (greater than 80% power) to prove that the difference is statistically significant, even if the rest of the data would indicate that there is no difference between two arms.

Stopping For Futility:

Sully et al. (15) suggested 30% CP to stop for futility, based on a simulation study. Table1 presents the hypothetical example and the estimation of CP which shows that how the trend is changing as the data is accumulated. As per Sully et al. (15) recommendation, we could stop the study for futility at the fourth interim analyses. However, if CPD is greater, as in third interim analysis in Table1 (CPD= 65%), the decision to stop the study for futility should be based on the opinion from the Data and Safety Monitoring Board (DSMB). Because, when the study was planned, there may have been good reasons to have a better efficacy for a new treatment. It means that if the study continues for some more time then they may get the expected difference. Though lower CPCT suggests stopping the study, there must be greater consensus to stop the study if the CPD is higher. If we do so, the future of interventions and research directions will have major setback. Therefore, the degree of evidence which is accepted by the medical community and the criterion for stopping the study for futility must be specified in the protocol at the planning stage.

Walter et al. (5) have made numerous recommendations based on their work. One of them was, if CP based on design would suggest continuation of the study, despite to stop the study based on CPCT then minimum measures to be considered such as, size of the trial, timing of interim analyses and criteria for stopping the study for futility. They also cautioned that the trials with futility stopping rules, but which continue to the completion will tend to overestimate the treatment benefit.

Uemura et al. (18) proposed a sample size re-estimation method based on 50%-CP method and compared it with the weighted Z-statistic. The modified 50%-CP method increases the sample size only when the CP based on the un-blind interim result is greater than 50%. Also, this method can control the type I error rate flexibly due to the restriction on the minimum required sample size.

Snapinn et al. (19) have mentioned that stopping a trial for futility is sometimes controversial, and when planning a trial, it is important for the study sponsor and DSMB to carefully consider whether or not the trial should include a futility rule. They have also stated that while stopping a trial for futility can save time and money, there is no violation of good ethical principles. They have suggested various methods to decide futility that are stochastic curtailment; predictive power is a partially Bayesian approach, and predictive probability (Bayesian approach).

In summary, if both CPCT is less than 30%, we recommend stopping the study for futility and if CPNull is greater than or equal to 80%, then stop the study for benefit.

Appendix I

Derivation of Conditional Power under Trend, Null, and Design:

Conditional Power:

The CP for two tailed test at level α is, (Proschan et al.)

$$CP(t) = 1 - \varphi\left(\frac{Z_{\frac{\alpha}{2}} - \left(b + I(1)^{\frac{1}{2}} \cdot \delta_{P^*}(1-t)\right)}{\sqrt{1-t}}\right) - - - - - (1)$$

Where,
φ(.) is cumulative normal distribution probability.

$Z_{\frac{\alpha}{2}}$ is critical value of Z at level $\frac{\alpha}{2}$ usually α=0.05 .

δ_F is the difference between the two arms to be observed in the rest of the trial.

$b = B(t) = \frac{I(\tau)\hat{\delta}(\tau)}{(I(1))^{\frac{1}{2}}}$ is Brownian motion at trial fraction t and is calculated from data observed difference at an interim analysis (4,6).

τ is the measure how far through the trial we are. (e.g: if total number of interim analysis is 5 then τ = 0.4 (2/5) at 2nd interim analysis)

$\hat{\delta}(\tau)$ difference between the two arms at the current interim analysis; t is a trial fraction $t = \frac{I(\tau)}{I(1)}$;

I(τ) is information statistics at a particular interim analysis (for example 2nd or 3rd interim analysis)

$$I(\tau) = \left(\sigma^2\left(\frac{1}{n_1}+\frac{1}{n_2}\right)\right)^{-1}$$

I(1) is information statistics at end of the trial $I(1) = \left(\sigma^2\left(\frac{1}{N_1}+\frac{1}{N_2}\right)\right)^{-1}$

where σ^2 is the variance used at the time of planning.

n1 and n2 are sample size available at the particular interim analysis (2nd or 3rd interim analysis).

N1 and N2 are total sample size planned.

Conditional Power under current trend:

CP_{CT} is computed by assuming the current observed treatment effect will continue in the future data $\delta_F = \hat{\delta}(\tau)$, where $\hat{\delta}(\tau)$, difference between the two arms observed so far.

Under the current trend $\delta_F = \hat{\delta}(\tau)$, therefore substitute $\delta_F = \hat{\delta}(\tau)$ and $\hat{\delta}(\tau) = \frac{(I(1))^{\frac{1}{2}} * b}{I(\tau)}$ (from equation Brownian Motion b) and we will get

$$CP(t) = 1 - \varphi\left(\frac{Z_{\frac{\alpha}{2}} - \left(\frac{b}{\tau}\right)}{\sqrt{1-t}}\right) - - - - - (2)$$

Conditional Power under Null:

CPNull is computed by assuming that there is no treatment effect in the future data. As per the assumption substitute δ_F=0 in equation (1), then the term $I(1)^{\frac{1}{2}} * 0 * (1-t)$ get vanished.

$$CP_{Null} = 1 - \varphi\left(\frac{Z_{\frac{\alpha}{2}} - b}{\sqrt{1-t}}\right) - - - - - (3)$$

Conditional Power under Design:

CPD is calculated by assuming that the future data will be generated as specified in the initial study design $(\delta_F = \delta_D)$ where δ_D is difference between the treatment and control group at the planning stage

$$CP_D = 1 - \varphi\left(\frac{Z_{\frac{\alpha}{2}} - \left(b + I(1)^{\frac{1}{2}}\delta_D(1-t)\right)}{\sqrt{1-t}}\right) - - - - - (4)$$

Appendix: II

Conditional power calculation:

Conditional power calculation for the study 1 was demonstrated below for the calculation purpose.

Planning parameters
Test=one sided test

Alpha=0.05; Beta=0.15

Required sample size in Arm A (N1) = 50
Required sample size in Arm B (N2) = 50
Response rate in Arm A (P1) =0.40
Response rate in Arm B (P2) =0.15

Interim parameters
Sample size in Arm A (n1) = 26
Sample size in Arm B (n2) = 26
Response rate in Arm A (p1) = 0.18
Response rate in Arm B (p2) = 0.13

Calculation:

$$\hat{\delta}(\tau) = p_1 - p_2 = 0.18 - 0.13 = 0.05$$

$$\bar{p} = \frac{p_1 + p_2}{2} = 0.155$$

$$\hat{\sigma}^2 = \bar{p} * (1 - \bar{p}) = 0.155 * (1 - 0.155) = 0.131$$

$$I(\tau) = \left(\sigma^2\left(\frac{1}{n_1}+\frac{1}{n_2}\right)\right)^{-1} = \left(0.131\left(\frac{1}{26}+\frac{1}{26}\right)\right)^{-1} = 99.237$$

$$I(1) = \left(\sigma^2\left(\frac{1}{N_1}+\frac{1}{N_2}\right)\right)^{-1} = \left(0.131\left(\frac{1}{50}+\frac{1}{50}\right)\right)^{-1} = 190.840$$

$$t = \frac{I(\tau)}{I(1)} = \frac{99.237}{190.840} = 0.520$$

$$Z(t) = \frac{\hat{\delta}(\tau)}{var\{\hat{\delta}(\tau)\}^{\frac{1}{2}}} = I(\tau)^{\frac{1}{2}}\hat{\delta}(\tau) = (99.237)^{\frac{1}{2}} * 0.05 = 0.498$$

$$b = B(t) = t^{\frac{1}{2}}Z(t) = (0.520)^{\frac{1}{2}} * 0.498 = 0.359$$

Conditional power under the null:

$$CP_{Null}(t) = 1 - \varphi\left(\frac{Z_{\frac{\alpha}{1}} - b}{\sqrt{1-t}}\right)$$

$$CP_{Null}(0.758) = 1 - \varphi\left(\frac{Z_{\frac{0.05}{1}} - 0.359}{\sqrt{1-0.520}}\right) = 1 - \varphi\left(\frac{1.645 - 0.359}{0.693}\right)$$

$$CP_{Null}(0.758) = 1 - \varphi\left(\frac{1.286}{0.693}\right) = 1 - \varphi(1.856) = 1 - 0.9683 = 0.0317 = 3.17\%$$

Conditional Power Under The Current Trend:

$$CP_{CT}(t) = 1 - \varphi\left(\frac{Z_{\frac{\alpha}{1}} - b/t}{\sqrt{1-t}}\right)$$

$$CP_{CT}(0.758) = 1 - \varphi\left(\frac{Z_{\frac{0.05}{1}} - \frac{0.359}{0.520}}{\sqrt{1-0.520}}\right) = 1 - \varphi\left(\frac{1.645 - 0.690}{0.693}\right)$$

$$CP_{CT}(0.758) = 1 - \varphi\left(\frac{0.955}{0.693}\right) = 1 - \varphi(1.378) = 1 - 0.9159 = 0.0841 = 8.41\%$$

Conditional Power Under The Design:

$$\delta_D = P_1 - P_2 = 0.25$$

$$CP_D(t) = 1 - \varphi\left(\frac{Z_{\frac{\alpha}{1}} - \left(b + I(1)^{\frac{1}{2}} * \delta_D * (1-t)\right)}{\sqrt{1-t}}\right)$$

$$CP_D(0.758) = 1 - \varphi\left(\frac{Z_{\frac{0.05}{1}} - \left(0.359 + (190.840)^{\frac{1}{2}} * 0.25 * (1 - 0.520)\right)}{\sqrt{1-0.520}}\right)$$

$$= 1 - \varphi\left(\frac{1.645 - 2.02}{0.693}\right)$$

$$CP_D(0.758) = 1 - \varphi\left(\frac{-0.375}{0.693}\right) = 1 - \varphi(-0.541) = 1 - 0.2943 = 0.7057 = 70.57\%$$

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