Terumo Medical Corporation

Cross-Seal IDE Trial: Prospective, Multi-Center, Single-Arm Study of the Cross-Seal Suture-Mediated Vascular Closure Device System

Protocol: TIS2018-01

Statistical Analysis Plan Amendment 1.4

August 5, 2020

Version History

Version	Version Date	Author/Title	Summary of Key Changes
Amendment 1.1 to SAP V. 1.2	May 29, 2020	Roseann White, Senior Principal Statistician	This document is an amendment to SAP version 1.2 makes the following changes from version 1.1: • clarifies the analysis populations to assure that they are consistent with the protocol and address the challenges in enrollment and follow up in during the COVID-19 pandemic. • Modifies the primary safety and efficacy endpoint analysis to address the challenges of conducting a clinical trial just before and during the pandemic per "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic", finalized March 2020. • Additional details about the

			statistical analysis
Amendment 1.2 to SAP V. 1.3	June 15, 2020	Roseann White, Senior Principal Biostatistician	This document is an amendment to SAP version 1.3 makes the following changes from version 1.2: 1. Corrected typos where FAS and PPS were reversed 2. Clarified the language for the number enrolled, 3. Updated the 80% power number for Primary Safety Endpoint to 81
Version 1.3 to Version 1.4	August 5, 2020	Roseann White, Senior Principal Biostatistician	Section 2: Abbreviation table corrected for PPAS_RI and FAS_RI Section 6: Sample sizes calculation section was expanded to include a range of sample sizes based on power

			Section 7.2.5: was modified as follows: • The efficacy analysis set will be the only analysis set to be used for the efficacy analysis. It will either consist of the PPS patients or PPS & PPS_RI patients • The last 18 sequentially enrolled PPS roll in patients will be used if needed Section 7.2.6: was modified as follows: • The safety analysis set will be the only analysis set to be used for the safetty analysis. It will either consist of the FAS patients or FAS & FAS_RI patients • The last 18 sequentially enrolled FAS rollin patients will be used if needed Section 7.3 has been modified to include the sites with < 5 patients enrolled into the geographically

			nearest site. Section 7.71 had the following changes: • Removed all reference to shaprio wilk and testing for normality • Updated the text to refer to the efficacy analysis set only • Updated the sensitivity analyses to reflect the revised efficacy analysis set approach and added a sensitivity analysis that includes a combination of both efficacy analysis set and PPS_RI Section 7.72 had the following changes: • Updated the text to refer to the safety analysis set only • Updated the sensitivity analyses to reflect the revised safety analysis set approach and added a sensitivity analysis that includes a combination of both safety

			analysis set and FAS_RI Section 7.8 was updated to refer to the safety and efficacy analysis set Section 9.0 added to provide the PASS output

Document Approval

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Table of Contents

1 Rationale for Amending SAP version 1.3

The SAP was updated to address the FDA's feedback on version 1.3.

2 List of Abbreviations and Definitions of Terms

Abbreviation/ Term	Definition
AE	Adverse Event
CIP	Clinical Investigation Plan
eCRF	Electronic Case Report Form
DUS	Duplex Ultrasound

Abbreviation/ Term	Definition
FAS	Full Analysis Set
FAS_RI	Full Analysis Dataset of roll-in patients
PG	Performance Goal
PPS	Per-Protocol Analysis Set
PPS_RI	Per-Protocol Analysis Set of roll-in patients
SAP	Statistical Analysis Plan
TTH	Time-to-hemostasis

3 Study Objectives

The study objective is to demonstrate the safety and efficacy of the investigational device to achieve hemostasis of common femoral artery access site in subjects undergoing percutaneous endovascular procedures utilizing 8-18Fr introducer sheath at the time that the enrollment was discontinued due to the COVID 19 pandemic.

4 Study Design

This trial is a prospective, multi-center, single-arm, clinical study. Subjects will undergo percutaneous endovascular procedure utilizing 8-18Fr introducer sheath and be treated with the investigational device for arteriotomy closure. A subject is considered enrolled in the study if the subject has signed the Informed Consent Form (ICF) and meets all eligibility criteria, including intra-procedural criteria.

5 Endpoint Definitions

This clinical study will evaluate the primary and secondary endpoints described below.

5.1 Primary Endpoints

5.1.1 Primary Safety Endpoint:

The primary safety endpoint is defined as freedom from major complications of the target limb access site within 30 days post-procedure. Major complications include the following:

1. Vascular injury attributable to the investigational device that requires surgical repair, stent-graft, or balloon angioplasty
2. Access site-related bleeding attributable to the investigational device that requires transfusion
3. Any new access site-related ipsilateral lower extremity ischemia attributable to the investigational device and documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram
4. Surgery for access site-related nerve injury attributable to the investigational device
5. Permanent (lasting > 30 days) access site-related nerve injury attributable to the investigational device
6. Access site infection requiring intravenous antibiotics and/or extended hospitalization

5.1.2 Primary Efficacy Endpoint

The definition of the primary efficacy is the mean time to hemostasis (TTH) in the common femoral artery (CFA) of the target limb access site with the use of the investigational device.

TTH will be evaluated from the time of procedural sheath removal to first observed cessation of CFA bleeding (excluding cutaneous or subcutaneous oozing at access site) in the target limb for subjects not requiring adjunctive intervention.

If a sheathless system is used during the procedure, TTH will be calculated from final introducer sheath removal to first observed cessation of CFA bleeding (excluding cutaneous or subcutaneous oozing at access site) in the target limb.

5.2 Secondary Endpoints

5.2.1 Secondary Safety Endpoints:

- The freedom from minor complications at the target limb access site within 30 days post-procedure. Minor complications which include the following:
  - Non-treated pseudoaneurysm attributable to the investigational device and documented by DUS
  - Pseudoaneurysm attributable to the investigational device and treated with ultrasound-guided compression, ultrasound-guided thrombin injection. or ultrasound-guided fibrin adhesive injection
  - Non-treated or treated arteriovenous (AV) fistula attributable to the investigational device and documented by DUS
  - Access site hematoma greater than or equal to 10 cm in diameter, attributable to the investigational device, and confirmed by DUS
  - Late (following hospital discharge) access site-related bleeding in the target limb
  - Lower extremity arterial emboli attributable to the investigational device
  - Vein thrombosis attributable to the investigational device
  - Transient access site-related nerve injury attributable to the investigational device
  - Access site wound dehiscence
  - Access site infection treated with intramuscular or oral antibiotics
- Device Related Complications (DRCs) and procedural complications within 30 days post-procedure
- Evaluation of all Adverse Events (AEs) from time of investigational device use within 30 days post-procedure, and through 60 days post-procedure for the subject's requiring a repeat DUS, including major and minor complications

5.2.2 Secondary Efficacy Endpoints:

- Technical Success: defined as the achievement of hemostasis with the investigational device without the need for any access-site-related adjunctive surgical or endovascular intervention (target limb only).
- Access site closure success: defined as technical success and freedom from major

complications within 48 hours of the index procedure or hospital discharge, whichever occurs first (target limb only).

- Treatment Success: defined as technical success and freedom from major complications through 30 days follow-up.
- Subjects requiring adjunctive surgical or endovascular intervention to achieve hemostasis of the access site (target limb only), including the type of adjunctive intervention.
- Subjects receiving adjunctive manual compression following the use of the investigational device to achieve hemostasis of the access site (target limb only). Adjunctive manual compression is defined as:
- Type of compression applied (light or firm, where light compression is defined as non-occlusive (i.e., "patent hemostasis"), allowing distal blood flow, and firm compression defined as occlusive prohibiting distal blood flow.
- Time-to-Ambulation: defined as the elapsed time from final procedural sheath removal to time when the subject stands and walks at least 20 feet without re-bleeding.
- Time-to-Discharge (i.e., time of actual discharge defined as the elapsed time between final procedural sheath removal and when the subject is discharged from the hospital)

- Occurrence of device failure. Device Failures may include the following:
- Device used in study subject resulting in the occurrence of a major complication
- Unable to use RESET 1 Button
- Unable to deploy PLUNGER on device
- Unable to use RESET 2 Button

5.2.3 Exploratory Endpoints

- Time-to-Device-Deployment defined as the time of guidewire removal during device insertion to time of guidewire reinsertion during device removal, and overall

procedure time defined as the time of first skin nick/incision to the achievement of hemostasis in the access site (target limb only)

- Time-to-Dischargeability (i.e., discharge eligibility defined as the elapsed time between final procedural sheath removal and time when the subject is medically able to be discharged based solely on the assessment of the access site as determined by the investigator.

6 Sample Size Determination

The sample size calculations were performed using PASS 2020 Version 20.0.2[1]. The appendix included the output from the software. The sample size for the study is based on power considerations for the primary effectiveness endpoint. As will be described below, this sample size should also provide adequate power for the primary safety endpoint.

6.1 Primary Efficacy Endpoint

The primary effectiveness hypothesis will be tested by comparing the primary effectiveness endpoint, mean time-to-hemostasis (TTH), against a performance goal (PG) of 15 minutes.

The comparison to the performance goal will be based on the following statistical hypothesis test:

$$H_0: \mu_{TTH} \geq 15$$

$$H_A: \mu_{TTH} < 15$$

where $\mu_{TTH}$is the mean time-to-hemostasis in minutes.

The test will be based on whether the upper one-sided 97.5% confidence limit (based on a t-distribution)[2] is less than 15. Assuming similar performance to Perclose ProGlide®, with a mean time-to-hemostasis of 9.8 minutes and a standard deviation of 17 minutes the sample sizes for power levels from 80 to 90%

a Table 1: Primary Efficacy Endpoint Sample Sizes for Various levels of Power

Power	Sample Size	Maximum Observed Time (minutes) and still reject H_0
80.0%	86	10.8
81.4%	89	10.9
82.3%	91	10.9
83.1%	93	10.9
84.3%	96	11.0
85.0%	98	11.1

Successful rejection of the null hypothesis will mean that the PG has been met.

6.1.1 Development of the Performance Goal

The PG was derived from literature for the Perclose ProGlide® (Abbott Vascular, Inc., Redwood City, CA, USA), a suture-mediated device indicated for the closure of large arterial access sites.

6.2 Primary Safety Endpoint

The primary safety hypothesis will be tested by comparing the primary safety endpoint, freedom from major complications of the target limb access site within 30 days post-procedure, against a performance goal.

The comparison to the performance goal will be based on the following statistical hypothesis test:

$$H_0: p \leq 85.2\%$$

$$H_A: p > 85.2\%$$

where *p* is the safety endpoint rate for the test device.

Assuming similar performance as ProGlide (an event-free rate of 94%), one-sided alpha = 0.05, the sample sizes for various levels of power are:

Table 2: Primary Safety Endpoint Sample Sizes for Various levels of Power

Power	Sample Size	Minimum # of Event Free Patients needed to reject the H_0
81.3%	78	72
85.6%	86	79
88.3%	95	87

6.2.1 Development of the Performance Goal

The observed rate of major complications for ProGlide was 6% (3/50), with a one-sided exact binomial upper 95% confidence bound of 14.8%. In terms of an event-free rate, these quantities are mathematically equivalent to an observed event-free rate of 94% with a lower confidence bound of 85.2%. Accordingly, for the current study, a value of 85.2% is proposed for a performance goal for the primary safety endpoint based on the event-free rate.

7 Statistical Analyses

7.1 General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analyses will be conducted using {SAS version 9.3 or later (SAS Institute Inc., Cary, NC)} or other widely accepted statistical or graphical

software as required.

7.1.1 Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and exact binomial method for categorical variables.

7.1.2 Study Visit

Study visit Day 0 is the date of the index procedure. Day in the study will be calculated relative to the index procedure as follows:

Study Day = Assessment Date – Index Procedure Date

Each subject duration in the study will be based on the last study contact date, which is the latest date of all follow-up visits, assessments, adverse event onset or resolution, and study exit, including date of death.

Duration will be calculated as follows: Duration Days = Start Date – End Date

7.1.3 Visit Windows

Unless otherwise specified, visit assessments will be analyzed for each analysis time point according to the visit entered in the electronic Case Report Form (eCRF).

7.1.4 Statistical Significance

Unless otherwise specified, hypothesis testing will be performed at the two-sided 0.05 significance level. P-values will be rounded to three decimal places. If a p-value is less than 0.001 will be reported as "<0.001". If a p-value is greater than 0.999, it will be reported as ">0.999".

7.1.5 Reporting Precision

Unless otherwise specified, the following conventions will apply for data display. In general, percentages will be displayed to 1 decimal place. Percentages <0.05% will be reported to 2 decimal places. For continuous parameters, means and medians will be reported to 1 additional decimal place than the measured value. In contrast, the standard deviation will be reported to 2 additional decimal places than the measured value. Minimum and maximum values will be reported to the same precision as the measured value.

7.2 Analysis Populations

7.2.1 Full Analysis Set

The full analysis set (FAS) as defined by the ICH E9[3] as "The set of subjects that is as close as possible to the ideal implied by the intention-to-treat principle." The guideline also defined the Intention-To-Treat Principle as the effect of a treatment policy can be best assessed by evaluating based on the intention to treat a subject (i.e., the planned treatment regimen) rather than the actual treatment given. Therefore, the FAS includes all patients that were consented, enrolled, and met the inclusion/exclusion criteria.

7.2.2 Per-Protocol Analysis Set

The protocol definition of the TTH endpoint includes only those patients that received the test device and did not have adjunctive therapy other than light compression applied to the access site manually, with a dressing, or as per the investigator's standard procedure for suture-mediated closure devices. Therefore, the per-protocol analysis set (PPS) includes those patients in the FAS where the patient received the test device and did not have adjunctive therapy other than light compression.

7.2.3 Full Roll-In Analysis Set

The full roll-in analysis set (FAS_RI) are those patients that meet the same criteria as the FAS but are identified as roll-in patients.

7.2.4 Per-Protocol Roll-In Analysis Set

The per-protocol roll-in analysis(PPS_RI) set are those patients that meet the same criteria as the PPS but are identified as roll-in patients.

7.2.5 Efficacy Analysis Set

Due to the challenges during the pandemic, the number of patients in a non-missing primary efficacy endpoint may drop below the lowest accepted power (80%) for approval trial design (< 86 patients). If the number of patients in the PPS is <= 86, the efficacy analysis set will include the patients in the PPS and the last 18 sequentially enrolled patients from the PPS_RI. If the number of patients in the PPS is > 86, then the efficacy analysis set will only include PPS patients.

7.2.6 Safety Analysis Set

Due to the challenges during the pandemic, the number of patients in a non-missing primary safety endpoint may drop below the lowest accepted power (80%) for approval trial design (< 78 patients). If the number of patients in the FAS is <= 78, the safety analysis set will include the patients in the FAS and the last 18 sequentially enrolled patients from the FAS_RI. If the number of patients in the FAS is > 78, then the safety analysis set will only include FAS patients.

7.3 Poolability Analyses

All investigational sites will follow the requirements of a common protocol and standardized data collection procedures and forms. The primary endpoints will be presented separately (major and minor complications will be presented separately for the primary safety endpoint) for each site using descriptive statistics. Poolability of the primary endpoints across the investigational site will be evaluated using a regression model with fixed effects for the site using the FAS for the primary safety endpoint and PPS for primary efficacy endpoint. Sites enrolling less than five subjects will be combined with the geographically nearest site. If the p-value for the site effect is <0.15,

additional exploratory analyses will be performed to understand any variations in outcomes by site.

7.4 Handling of Missing Data

All attempts will be made to limit the amount of missing data. For all analyses of the primary endpoints, the number of observations available, patients with no primary safety endpoint information, and patients with imputed results will be reported so the reader can assess the impact of missing data.

7.4.1 Imputation for Endpoints

Due to the challenges related to the COVID-19 pandemic faced during the enrollment, some 30-day follow-up visits were outside of the protocol specified window. Therefore, for those patients whose 30-day visit was outside the window, the primary safety endpoint will be imputed based on the on visits that occurred at a minimum of 23 days post-discharge and is the closest to the 30-day visit. If there were no post-discharge visits, the primary safety endpoint will be imputed based on the site contacting the patient by phone as well as reviewing their records to determine the patient's primary safety endpoint status at 30 days. If even that information is not available, then the patient will be considered as missing the primary safety endpoint data.

7.4.2 Sensitivity Analyses

Sensitivity analyses will be performed to assess the impact of missing data for the primary safety endpoint; a tipping point analysis will be conducted in which subjects censored without a 30 days follow-up visit are sequentially imputed as failures at the time of censoring. The primary safety endpoint analysis will be repeated after each sequentially imputed failure.

Sensitivity analyses will be performed to assess the impact of missing data for the primary efficacy endpoint; a tipping point analysis will be conducted in which subjects without a TTH are sequentially imputed as 15 minutes (the performance goal). The

primary efficacy endpoint analysis will be repeated after each sequentially imputed value.

7.4.3 Imputation for Dates

More generally, in the case of partial adverse event onset date or date of death, the unknown portion of the date of the event will be imputed. If the month and year are known, the 15th of the month will be used for analysis. If only the year is known, the event will be analyzed as if it occurred on June 30th of the known year. In the rare case that the date is fully unknown, the date will be imputed as the index procedure date. Imputation of partial dates is subject to the condition that it must occur on or after the index procedure date. In the case where the imputed date is before the index procedure date, the date of the index procedure will be used. As death cannot occur before any documented subject contact, for date of death, the imputed date of death must occur on or after the last known contact in the study.

7.5 Subject Disposition

Subjects who are screened and signed an informed consent form, but do not meet all protocol eligibility criteria (i.e., screening failure), will be excluded from the statistical analyses. These subjects will be summarized in a subject accountability table only.

Subject accountability will be summarized by visit for those in the FAS. The number of subjects who are enrolled, eligible for follow-up, and number completing clinical follow-up will be summarized for each protocol-required visit.

7.6 Demographics and Baseline Characteristics

Descriptive statistics will be presented for clinically relevant baseline demographic, medical history, and clinical characteristic variables.

7.7 Analysis of Study Endpoints

Study success is defined as the successful rejection of the corresponding null

hypotheses for each of the primary safety and effectiveness endpoints.

7.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be evaluated using the using the efficacy analysis set. The mean and standard error will be reported for the primary efficacy endpoint. A one-sample t-distribution will be used for calculating the upper 97.5% confidence limit.

Sensitivity Analyses

There will be three sensitivity analyses:

1. The primary efficacy endpoint analysis will be repeated with the PPS patients only if PPS_RI patients are added to the efficacy analysis set
2. Tipping analysis based on missing data in the efficacy analysis set as described in section 7.4.2
3. The primary efficacy endpoint analysis will be repeated with the PPS_RI and the efficacy analysis set combined.

7.7.2 Primary Safety Analysis

The primary safety endpoint will be evaluated using the FAS or the safety analysis set if roll-ins are needed. The endpoint will be presented as the proportion of subjects with freedom from primary safety endpoint and the lower 95% confidence limit using the Clopper-Pearson exact method[4]. If the one-sided 95% confidence limit is greater than 85.2%, then the device will have met the performance goal for safety.

Sensitivity Analyses

There will be three sensitivity analyses:

1. The primary safety endpoint analysis will be repeated with the FAS patients only if FAS_RI patients are added to the safety analysis set
2. Tipping analysis based on missing data in the safety analysis set, as described in section 7.4.2.

3. The primary efficacy endpoint analysis will be repeated with the FAS_RI and the safety analysis set combined.

7.7.3 Secondary Endpoints

No formal hypothesis tests for the secondary and exploratory endpoints will be performed; endpoints will be summarized using the FAS with descriptive statistics.

7.8 Subgroup Analyses

Subgroup analysis of the primary safety (major and minor complications analyzed separately) and efficacy endpoints will be performed for the following subgroups: gender, age (Age<65, Age≥65), and race (white vs. non-white). These analyses are intended to assess the consistency of results across subgroups.

Subgroup analyses will be performed using the efficacy analysis set for the primary efficacy endpoint and the safety analysis set for the primary safety endpoint. For each subgroup, a regression model will be fit that includes fixed effects for subgroup membership.

7.9 Interim Analyses

There are no formal plans for interim analyses for the purposes of early stopping for effectiveness or sample size adjustments. Interim safety reports will be performed as requested by the DSMB Charter. Unless otherwise specified, methods for such reports may follow those outlined in this document.

7.10 Protocol Deviations

Investigational sites will report deviations from the procedures outlined in the CIP on the eCRF. Protocol deviations will be summarized for all deviations and by type with event counts and number of subjects with at least one deviation.

8 Additional Changes to Planned Analyses

Any additional changes to planned statistical analyses determined necessary before

performing the analyses will be documented in an amended Statistical Analysis Plan Version 1.4 and approved before the analysis when possible. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

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[1] PASS 2020 Power Analysis and Sample Size Software (2020). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

[2] Dawson, B., & Trapp, R. G. (2004). *Basic & clinical biostatistics (4th ed.)*. New York: Lange Medical Books-McGraw-Hill, chapter 5

[3] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (1998), *ICH Harmonised Tripartite Guideline Statistical Principles For Clinical Trials E9*, retrieved from https://database.ich.org/sites/default/files/E9_Guideline.pdf

[4] Clopper, C.; Pearson, E. S. (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 26 (4): 404–413. doi:10.1093/biomet/26.4.404.

9 APPENDIX – PASS 2020 Output

9.1 Primary Efficacy Endpoint

PASS 2020, v20.0.2 8/7/2020 11:40:19 AM 1

One-Sample T-Tests for Non-Inferiority

Numeric Results

Higher Means are Worse
Hypotheses: H0: μ ≥ μ0 vs. H1: μ < μ0

Power	N	Non-Inferiority Mean μ0	Actual Mean μ1	Standard Deviation σ	Alpha	Beta
0.80080	86	15.0	9.8	17.0	0.025	0.19920
0.81436	89	15.0	9.8	17.0	0.025	0.18564
0.82296	91	15.0	9.8	17.0	0.025	0.17704
0.83120	93	15.0	9.8	17.0	0.025	0.16880
0.84294	96	15.0	9.8	17.0	0.025	0.15706
0.85037	98	15.0	9.8	17.0	0.025	0.14963

References

Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

Julious, Steven A., 2004. 'Tutorial in Biostatistics. Sample sizes for clinical trials with Normal data.' Statistics in Medicine, 23:1921-1986.

Report Definitions

Power is the probability of rejecting the null hypothesis when it is false. It should be close to one.
N is the sample size, the number of subjects (or pairs) in the study.
μ0 = μR + NIM is the non-inferiority mean since higher means are worse, where μR is the baseline, standard, or reference mean, and NIM is the margin of non-inferiority.
μ1 is the actual value of the population mean at which power and sample size are calculated.
σ is the standard deviation of the response (or standard deviation of differences for paired data). It measures the variability in the population.
Alpha is the probability of rejecting the null hypothesis when it is true, which is the probability of a false positive.
Beta is the probability of accepting the null hypothesis when it is false, which is the probability of a false negative.

Summary Statements

A sample size of 86 achieves 80% power to detect non-inferiority using a one-sided one-sample t-test when the
non-inferiority mean is 15.0 and the actual mean is 9.8. The data are drawn from a single population with an estimated standard deviation of 17.0. The significance level (alpha) of the test is 0.025.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
10%	86	96	10
10%	89	99	10
10%	91	102	11
10%	93	104	11
10%	96	107	11
10%	98	109	11

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One-Sample T-Tests for Non-Inferiority

Definitions

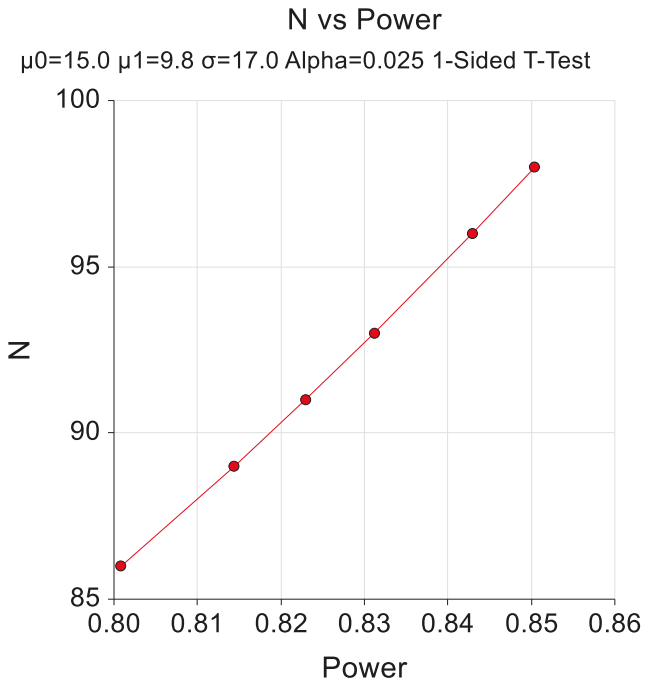
Dropout Rate (DR) is the percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e. will be treated as "missing").

N is the evaluable sample size at which power is computed. If N subjects are evaluated out of the N' subjects that
are enrolled in the study, the design will achieve the stated power.

N' is the total number of subjects that should be enrolled in the study to end up with N evaluable subjects, based on the assumed dropout rate. After solving for N, N' is calculated by inflating N using the formula N' = N /
(1 - DR), with N' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H.,
and Lokhnygina, Y. (2018) pages 32-33.)

D is the expected number of dropouts. D = N' - N.

Chart Section



One-Sample T-Tests for Non-Inferiority

Procedure Input Settings

Autosaved Template File
C:\Users\Roseann White\Documents\PASS 2020\Procedure Templates\Autosave\One-Sample T-Tests for Non-Inferiority - Autosaved 2020_8_7-11_40_19.t204

Design Tab

Solve For:	Sample Size
Higher Means Are:	Worse (H1: μ < μ0)
Population Size:	Infinite
Power:	.8 to .85 by 0.01
Alpha:	.025
μ0 (Non-Inferiority Mean):	15
μ1 (Actual Mean):	9.8
σ (Standard Deviation):	17

9.2 Primary Safety Endpoint

Non-Inferiority Tests for One Proportion

Numeric Results for Testing Non-Inferiority of One Proportion using the Exact Test

Higher Proportions are Better
Alternative Hypothesis: One-Sided (H0: P ≤ P0 vs. H1: P > P0)

Power*	Baseline Proportion n	PB	Non-Inf. Difference d0	d1	Actual Difference Alpha	Alpha*	Target If R ≥	Actual Reject H0
0.81297	78	0.9400	-0.0880		0.0000	0.050	0.046	72
0.81297	78	0.9400	-0.0880		0.0000	0.050	0.046	72
0.85580	86	0.9400	-0.0880		0.0000	0.050	0.049	79
0.85580	86	0.9400	-0.0880		0.0000	0.050	0.049	79
0.85580	86	0.9400	-0.0880		0.0000	0.050	0.049	79
0.85580	86	0.9400	-0.0880		0.0000	0.050	0.049	79

* Power and actual alpha were computed using binomial enumeration of all possible outcomes.

References
Blackwelder, W.C. 1998. 'Equivalence Trials.' In Encyclopedia of Biostatistics, John Wiley and Sons. New York.
Volume 2, 1367-1372.

Chow, S. C., Shao, J., and Wang, H. 2008. Sample Size Calculations in Clinical Research, Second Edition.
Chapman & Hall/CRC. Boca Raton, Florida.
Fleiss, J. L., Levin, B., and Paik, M.C. 2003. Statistical Methods for Rates and Proportions. Third Edition. John
Wiley & Sons. New York.

Report Definitions

Power is the probability of rejecting the null hypothesis when it is false. It should be close to one.
n is the size of the sample drawn from the population. To conserve resources, it should be as small as possible.
PB is the baseline or standard value of the proportion.
d0 = P0-PB is the distance below PB that is still considered non-inferior.
d1 = P1-PB is the value of the difference at which the power is calculated.
Alpha (significance level) is the probability of rejecting the null hypothesis when it is true. It should be small.
Target Alpha is the significance level that the study design is meant to achieve.
Actual alpha is the significance level that is actually achieved by the design.
Reject H0 If... gives the critical value(s) for the test.

Summary Statements

A sample size of 78 achieves 81.297% power to detect a non-inferiority difference (P0-PB) of -0.0880 using a
one-sided exact test with a target significance level of 0.050. The actual significance level achieved by this test is
0.046. These results assume a baseline proportion (PB) of 0.9400 and that the actual difference (P1-PB) is
0.0000.

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Non-Inferiority Tests for One Proportion

Dropout-Inflated Sample Size

Dropout Rate	Sample Size n	Dropout-Inflated Enrollment Sample Size n'	Expected Number of Dropouts D
10%	78	87	9
10%	78	87	9
10%	86	96	10

10%	86	96	10
10%	86	96	10
10%	86	96	10

Definitions

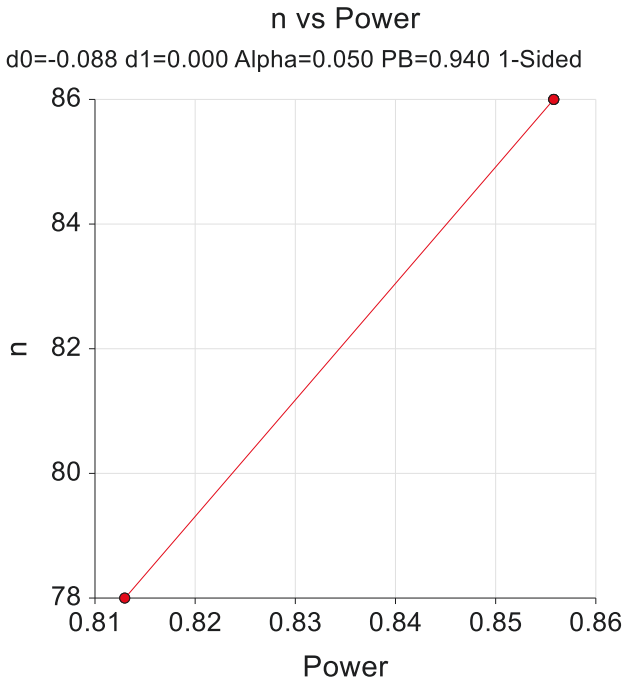
Dropout Rate (DR) is the percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e. will be treated as "missing").

n is the evaluable sample size at which power is computed. If n subjects are evaluated out of the n' subjects that are enrolled in the study, the design will achieve the stated power.

n' is the total number of subjects that should be enrolled in the study to end up with n evaluable subjects, based on the assumed dropout rate. After solving for n, n' is calculated by inflating n using the formula n' = n / (1 - DR), with n' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. (2018) pages 32-33.)

D is the expected number of dropouts. D = n' - n.

Chart Section



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Non-Inferiority Tests for One Proportion

Procedure Input Settings

Autosaved Template File
C:\Users\Roseann White\Documents\PASS 2020\Procedure Templates\Autosave\Non-Inferiority Tests for One Proportion - Autosaved 2020_8_7-11_35_53.t352

Design Tab
Solve For: Sample Size
Power Calculation Method: Binomial Enumeration
Max n for Binomial Enumeration: 10000
Higher Proportions Are: Better (H1: P > P0)
Test Type: Exact Test
N (Population Size): Infinite
Power: 0.80 to 0.85 by 0.01
Alpha: .05
Input Type: Differences
PB (Baseline Proportion): .94
d0 (Non-Inferiority Difference): -0.088
d1 (Actual Difference): 0