Use of a passive disinfection device to improve the disinfection compliance of connectors and to reduce Blood Stream Primary Infection associated with central catheters (CLABSI) in an adult oncology hospital

Statistical Analysis Plan

Version No. 3.0

24 July 2019

Prepared by:

[redacted]

Requested by:

3M Brazil

[redacted]

TITLE PAGE

Study title:	Use of a passive disinfection device to improve the disinfection compliance of connectors and to reduce Blood Stream Primary Infection associated with central catheters (CLABSI) in an adult oncology hospital
Study code:	Protocol CLIN-PROT-ICH-US-05-319980
Study type:	Quasi-experimental study
Study device	3M™ Curos™ Disinfecting Cap for Needleless Connectors
Therapeutic area:	Hospital-acquired infections
Sponsor:	3M Brazil
	[redacted]
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Statistical analysis plan performed by:	[redacted]

SIGNATURE PAGE

STUDY TITLE: Use of a passive disinfection device to improve the disinfection compliance of connectors and to reduce Blood Stream Primary Infection associated with central catheters (CLABSI) in an adult oncology hospital

PROTOCOL VERSION: Version 8

PROTOCOL DATE: 28February2019

SAP PREPARED BY:

_____ _____/_____/_____

[redacted]

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SAP REVIEWED BY:

_____ _____/_____/_____

[redacted]

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SAP REVIEWED AND APPROVED BY:

_____ _____/_____/_____

[redacted]

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REVISION LOG

Version No.	Version Date	Author	Changes from Previous Approved Versions
1.0	09 January 2019	[redacted]	Not Applicable (First Version)
2.0	03 April 2019	[redacted]	Update of SAP according to the new protocol version (No.8 28February2019) – A new ad-hoc analysis was add to the study to further classify CLABSI events into those attributable to mucosal barrier injury (MBI) and into non-MBI associated infections
3.0	24 July 2019	[redacted]	New clarifications in sections “6. Definition of analysis subsets” and “9. Data, derivations and transformations”

TABLE OF CONTENTS

1 RATIONAL

This Statistical Analysis Plan (SAP) was written in accordance with [redacted] and intends to provide guidelines from which the analysis will proceed, create a common and clear understanding of the planned analysis by all involved, clarify issues which were not clarified in the protocol, expand statistical section of the protocol, provide basis for the statistical section of the statistical report and reduce the opportunity for bias by prospectively defining analysis. This SAP was prepared by the biostatistician who will be further responsible (if possible) for the statistical analysis of the study data. This biostatistician was not involved in the release of the randomization list of this trial and will be maintained blinded to treatments until the final database is locked.

This SAP, in particular table shells and examples of figures/graphs, was reviewed and approved by the Sponsor's Representative previously to database locking and performance of the statistical analysis.

Any changes to the planned statistical methodology here defined during the statistical analysis of the study data will be documented in the Statistical Report and in the Study Clinical Report.

This document was written in accordance with the information contained in the Study Protocol CLIN-PROT-ICH-US-05-319980, version 8, of 28 February 2019 and CRF (Case Report Form) Version 6, 03 April 2019.

2 STUDY OBJECTIVES AND ENDPOINTS

The objective of this quality improvement project is to replicate hub disinfection compliance studies in a Brazilian model, where etiology of infections differ from many northern countries. Completing this quality improvement project will help determine if there is a corresponding drop in CLABSI when using disinfecting barrier caps as in seen in the studies referenced above, given the differences in causative organisms for CLABSI.

2.1 Objectives

- To examine healthcare professionals' compliance to needleless connector antisepsis with the barrier cap protocol compared to the previous "scrub the hub" protocol;

- To establish the effect of the disinfecting barrier cap on the rate of Central Line Associated Blood Stream Infection (CLABSI) per 1,000 intravenous line days among the designated patient population.

Catheter-associated urinary tract infection (CAUTI) rates and ventilator-associated pneumonia (VAP) rates during the intervention period will also be reviewed to control for possible seasonal or environmental effects that may also influence CLABSI and hospital infection rates overall.

2.2 Endpoints

Primary endpoint

The rate of compliance to hub disinfection protocol.

Secondary endpoints

- Rate of central line associated bloodstream infections (CLABSIs) per 1,000 central line days;
- Catheter-Associated Urinary Tract Infection (CAUTI) per 1,000 catheter days and Ventilator-Associated Pneumonia (VAP) per 1,000 ventilator days (controls).

3 STUDY DESIGN

A quasi-experimental before-and-after project with a seven -month intervention phase.

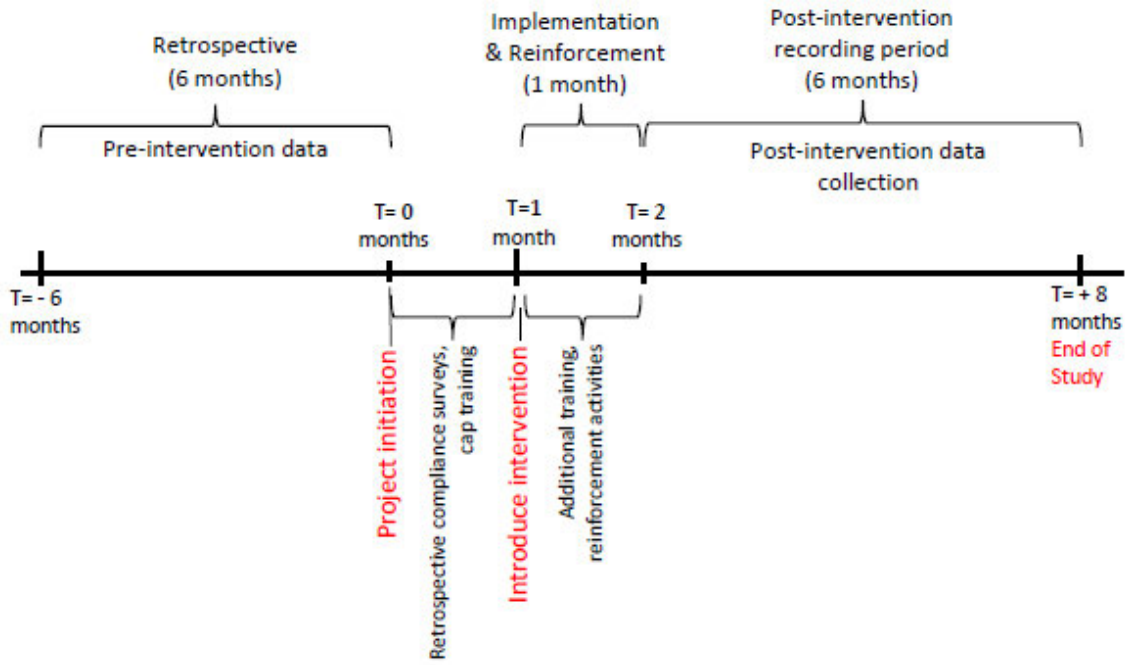

Figure 1 – Study design

4 STUDY POPULATION

During the project, no individual patient health information will be collected.

4.1 Subject Inclusion Criteria

- Adult patients admitted to the participant oncologic hospital
- Adult patients in the assigned intervention units during the seven-month intervention period who require needleless connectors for Central Venous Catheters (CVC) IV tubing access.

  The types of central venous catheters accessed by needleless connectors in this study include:

  - Non-tunneled CVCs percutaneously inserted into the internal jugular, subclavian, or femoral veins;
  - Tunneled CVCs implanted in the internal jugular, subclavian, or femoral veins;
  - Peripherally inserted central catheters (PICCs) inserted percutaneously into the basilic, brachial, or cephalic vein and entering the superior vena cava.
  - Patients without CVC IV access who are using a three-lumen dialysis catheter with a needleless connector on the third lumen. If a patient with a dialysis catheter but without CVC IV access presents an infection, the infection will be counted nonetheless due to the impossibility of separating it from the other infections. Dialysis catheters will only receive the disinfecting cap if the dialysis catheter contains a third lumen with a needleless connector attached.
  - Patients meeting inclusion criteria and who are subsequently transferred out to a unit of the hospital not covered by the study will have disinfecting caps removed immediately before transfer and will not be included in the compliance audits during their period out of the study unit. They will continue to be evaluated when they return to the study unit if that ever occurs. Therefore, if these patients are then transferred back from those units (includes HSR units such as: Surgical Center, Nuclear Medicine, Radiotherapy, Center of Diagnosis and Imaging, and Chemotherapy; and other hospitals of the complex: [redacted]), disinfecting caps will be re-introduced upon patient transfer, and patients will again be included in the study.

4.2 Subject Exclusion Criteria

- Adult patients admitted to the participant oncologic hospital during the seven-month intervention period that do not require needleless connectors for CVC IV access during their hospital stay.
- Patients without CVC IV access who are using two-lumen dialysis catheters. If such a patient presents an infection, it will be counted nonetheless due to the impossibility of separating it from the other infections. Dialysis catheters will only receive the caps if the dialysis catheter contains a third lumen, with a needleless connector.
- Patients may be excluded from the study at the investigator's discretion in case of unforeseen circumstances.
- Additionally, patients who require needleless connectors for CVC IV access, who are subsequently transferred to a different institution or to a different ward/unit that has not been trained in the use of disinfecting barrier caps, will be excluded from the study beginning at the time of transfer. For these patients, the disinfecting caps will be removed immediately before the patient is transferred to a unit of the hospital not covered by the study (includes HSR units such as: Surgical Center, Nuclear Medicine, radiotherapy, diagnostic center and imaging, and chemotherapy); and other hospitals of the complex: [redacted]). In the hospital units (wards) not covered by the study, the procedure used for the disinfection of the catheters will be the standard procedure of the hospital (scrub-the-hub) instead of the disinfecting caps.

5 PROTOCOL CLARIFICATIONS

In the protocol infections analysis were classified as efficacy analysis. Since this is a real-world study, in this SAP, these analyses will be classified as "Effectiveness analysis" instead of "Efficacy analysis".

In the effectiveness analyses, section 5.3.2 of the protocol, it is planned Poisson regressions for the measure rate of CLABSI and CAUTI/VAP per 1000 central line days with predictors sort of treatment (scrub-the-hub protocol or the disinfecting barrier cap), and variables for the time trend and the unit. In this SAP, it is planned two Poisson regressions for measure rate of CLABSI with all covariables (time trend, unit and sort of treatment). For the second Poisson regression model, since time trend variable and sort of treatment variable are dependent variables, this model will just include sort of treatment and unit. CAUTI and VAP infections

were only collected for the ICU unit/ward, in consequence, Poisson regression models will be performed, if applicable, with time trend and sort of treatment covariables.

Compliance calculation method of the period previous the intervention (scrub-the-hub) and after intervention (prospective period – needleless connectors compliance audits) are presented in section 9 - Data, derivations and transformations.

Infection rates calculation are presented in section 9 - Data, derivations and transformations.

Compliance by format of disinfecting cap (disinfecting cap strips vs. individual disinfecting caps) of the post-intervention period (prospective period) will be assessed. The type of caps used during the study was limited by unit ward. Only ICU unit ward was allowed to use disinfecting barrier cap strips, because of that the ICU post-intervention period compliance and the disinfecting barrier cap strips compliance results will be identical. On the other hand, individual disinfecting caps compliance will be calculated by the other unit wards (2º floor, 3º floor, 3º floor – surgical ward, 4º floor and 5º floor). Please see section 9 Data, derivations and transformations.

In the protocol section 5.1 – Datasets Analyzed, CAUTI and VAP data from the six months prior to the intervention will be analyzed and compared to data in the 6-month post intervention recording period to determine product effectiveness. In this SAP, CAUTI and VAP will not be compared between the pre-intervention period and the prospective period, because CAUTI and VAP infections assessments were only collected for ICU unit. Due to the lack of infections assessments in these two periods, only descriptive statistics will be presented.

In the protocol, it is described that the prospective compliance will include the observations of the number of needleless connectors with, and the number of needleless connectors without, disinfecting barriers caps attached. In this SAP for the prospective compliance will include also the observations of applicable ports with misused caps. In section *9 Data, derivations and transformations* is presented the formula calculation for compliance rate for use of the disinfecting barrier cap on needleless connectors (post-intervention period).

In this SAP the CAUTI and VAP rates will be calculated using the number of CAUTI and VAP variables, instead of CLABSI variables as said in section 5.3.2 Efficacy Analysis of the protocol.

6 DEFINITION OF ANALYSIS SUBSETS

Data from all compliance audits within the six-month recording period (after the first month of intervention) will be analyzed for protocol compliance. This will be compared to compliance

before the intervention, which will be determined by the pre-intervention survey. All surveys from the pre intervention period will be included in the analysis.

CLABSI data from the six months prior to the intervention will be analyzed and compared to data in the 6-month intervention recording period to determine product effectiveness. This analysis will also be performed by MBI (mucosal barrier injury) and not MBI related. CAUTI, and VAP data from the six months prior to the intervention and in the 6-month intervention recording period will be analyzed.

Data from the "implementation and reinforcement" period, first month after the introduction of the intervention, will not be used for the compliance analyses of the primary endpoint and for the effectiveness analysis (secondary endpoints), since this is a training period and may produce bias in the results. However, these data will be summarized using descriptive statistics.

7 STATISTICAL METHODS

All data will be summarized using descriptive statistics namely mean, standard deviation, median, minimum and maximum for quantitative variables and counts and percentages for qualitative variables. Percentages will be calculated based on non-missing values.

All statistical tests will be two-tailed considering a significance level of 5%.

Statistical analysis will be conducted through the software SAS® (version 9.4; SAS Institute Inc, Cary, USA).

7.1 Handling missing data

There will be no imputation of missing data for this study, unless otherwise specified. In case of complete missing dates, date is to be considered as missing.

In case of partial dates, if applicable:

- Missing day is to be considered as the 15th day of the month;
- Missing day and month are to be considered as the 1st day of July.

7.2 Compliance Analyses

Compliance rates to scrub-the-hub disinfection procedures before the intervention will be determined by written survey. The target survey response rate on scrub-the-hub compliance is 70% of healthcare professionals in the intervention wards that utilize needleless connectors for patient IV access. An overall compliance rate and compliance rates per intervention ward will be determined.

The calculation method of the survey compliance rate is presented in section 9 - Data, derivations and transformations. Survey compliance will be assessed by the *scrub time* and *dry time* of the self-reported part of the survey.

Compliance rate for the use of the disinfecting barrier cap on needleless connectors during the intervention recording period will be determined by weekly observations in each assigned intervention ward, which will be scheduled to ensure the absence of a shift bias.

The calculation method of the use of the disinfecting barrier cap on needleless connectors compliance is presented in section 9 - Data, derivations and transformations.

Survey compliance rate and compliance rate for the use of the disinfecting barrier cap on needleless connectors during the intervention recording period by wards will also be assessed.

The Student's t-test for independent samples will be used to compare the compliance rate between pre and post intervention period. In case of no evidence of normality assumptions, the Mann-Whitney U test will be used instead of Student's t-test.

7.3 Effectiveness Analyses

7.3.1 CLABSI

The statistical analysis for effectiveness is a Poisson regression with outcome measure rate of CLABSI per 1,000 central line days and with predictors sort of treatment (scrub-the-hub protocol or the disinfecting barrier cap), unit (ward) and time trend.

This analysis will also be performed by CLABSI infections associated with mucosal barrier injury (MBI) and not MBI-related.

7.3.2 CAUTI/VAP

The statistical analysis for effectiveness is a Poisson regression with outcome measure rate of CAUTI/VAP per 1,000 central line days and with predictors sort of treatment (scrub-the-hub protocol or the disinfecting barrier cap) and time trend.

8 STATISTICAL RESULTS

8.1 Sample characterization

Sample characterization results will be presented in table 1 of the appendix.

8.2 Compliance for pre and post intervention period

The results regarding compliance survey of the pre-intervention period (scrub-the-hub) will be presented in table 2, listing 2 and listing 3 of the appendix.

Results regarding the compliance in the post-intervention period (use of the disinfecting barrier cap on needleless connectors) will be presented in table 15 and listing 1 of the appendix.

Results regarding compliance rate comparations between retrospective and prospective periods will be presented in table 16 of the appendix.

8.3 Infection assessments for the pre and post intervention period

The results regarding the infections assessments in the retrospective period (scrub-the-hub) and in the prospective period (use of the disinfecting barrier cap on needleless connectors) will be presented in tables 3 and 4 and listing 5 of the appendix.

CLABSI/CAUTI/VAP comparations between pre-intervention and prospective periods will be presented in table 5 of the appendix.

Poisson regression results model for predicting rate of CLABSI infections, and by MBI, will be presented in table 6, table 7, table 8, table 9, table 10 and table 11 of the appendix.

Poisson regression results model for predicting rate of CAUTI infections will be presented in table 12 of the appendix.

Poisson regression results model for predicting rate of VAP infections will be presented in table 13 of the appendix.

8.4 Changes to infection reduction practices

Changes to infection reduction practices will be presented in table 14 and listing 6 of the appendix.

8.5 Brainstorming

Brainstorming results will be presented in table 17 and in listing 4 of the appendix.

8.6 Compliance by format of disinfecting cap

Compliance by format of disinfecting cap (disinfecting cap strips vs. individual disinfecting caps) for the post-intervention period will be presented in table 18 of the appendix.

9 DATA, DERIVATIONS AND TRANSFORMATIONS

- **Scrub-the-hub survey compliance (retrospective period)**

Compliance of the scrub-the-hub (self-reported and coworkers) survey will be calculated through scrub time and dry time:

In each of the scrub time (Table 1) and dry time (Table 2) questions tables a calculation has to be made to provide the percent of the time that the clinician scrubs the hub (Table 1) 10 seconds or more or allows the hub to completely dry (Table 2).

Each answer has a percentage assigned for the calculation of compliance: “Always” = 100%; “Usually” = 75%; “Sometimes” = 25%; and “Never” = 0%.

Only the answers of “≥10 - <15 seconds” and “≥15 seconds” will be considered for the calculation of compliance, because physicians will only be compliant if scrub time is equal or more than 10 seconds. Therefore, in compliance calculation, scrub time for “No scrub”, “<5 seconds”, “≥5 - < 10 seconds” will be multiplied by zero.

For the example bellow (Table 1), compliance of scrub time will be calculated as follow:

$$\begin{array}{r} 0\% \times 0 \\ +\ 25\% \times 0 \\ +\ 75\% \times 0 \\ +\ 25\% \times 1 \\ \underline{+\ \ 0\% \times 1} \\ 25\ \% \end{array}$$

The first three rows values would then be multiplied by zero and the last two multiplied by 1. The percentage will then be totaled by summing all the percentages for each scrub time.

Table 1 – Scrub-the-Hub survey (scrub time table)

Scrub Time	Always (100%)	Usually (75%)	Sometimes (25%)	Never (0%)
No scrub	|__|	|__|	|__|	|_X_|
<5 seconds	|__|	|__|	|_X_|	|__|
≥5 - <10 seconds	|__|	|_X_|	|__|	|__|
≥10 - <15 seconds	|__|	|__|	|_X_|	|__|
≥15 seconds	|__|	|__|	|__|	|_X_|
If scrub time <10 seconds, indicate the most likely reason:		|__| The patient urgently needed the medication |__| High patient - nurse ratio |__| In my mind, I believe <10 seconds is more than necessary |__| Another reason: _____		

For dry time, compliance will be calculated as follow:

$$\begin{array}{r} 75\% \times 0 \\ \underline{+\ 25\% \times 1} \\ 25\ \% \end{array}$$

The first-row value would then be multiplied by zero and the last row multiplied by 1. The percentage will then be totaled by summing all the percentages for the two dry times.

Table 2 – Scrub-the-Hub survey (dry time table)

Dry Time	Always (100%)	Usually (75%)	Sometimes (25%)	Never (0%)
No dry	|__|	|_X_|	|__|	|__|
Completely dry	|__|	|__|	|_X_|	|__|

The total compliance for each physician will be calculated through the following formula:

$$Scrub - the - hub\ survey\ compliance\ (\%) = Scrub\ time\ compliance\ (\%) \times Dry\ time\ compliance\ (\%)$$

For the previous example, scrub-the-hub survey compliance rate was: 25% X 25%= **6,25%**

If missing data are present in scrub-the-hub survey, compliance will not be calculated for that subject.

Compliance rate will be calculated per physician.

- **Compliant clinician in scrub-the-hub survey (target compliance rate achieved)**

A dichotomous variable (yes/no) will be calculated.

Yes – clinician who meet compliance rate equal or higher than 70% in scrub-the-hub survey.
No – Otherwise

- **Compliance rate for use of the disinfecting barrier cap on needleless connectors (post-intervention period)**

The following formula must be considered for each shift and ward:

$$Compliance\ rate\ for\ use\ of\ disinfecting\ barrier\ cap\ on\ needleless\ connectors\ (\%) = \frac{No.of\ applicable\ capped\ ports\ (correclty\ used)}{No.applicable\ capped\ ports\ (correclty\ used) + No.applicable\ uncapped\ ports + No.applicable\ ports\ with\ missed\ caps} \times 100$$

If missing data are present in data compliance audits, for a shift/ward then that compliance will not be calculated for that shift/ward.

- **CLABSI rate per 1000 catheter/days**

The following formula must be considered:

$$CLABSI\ rate\ per\ 1000\ catheter\ line/days = \frac{Number\ of\ CLABSIs\ infections}{Number\ of\ central\ venous\ catheter\ (CVC)\ days} \times 1000$$

- **CAUTI rate per 1000 catheter/days**

The following formula must be considered:

$$CAUTI\ rate\ per\ 1000\ catheter/days = \frac{Number\ of\ CAUTIs\ infections}{Number\ of\ indwelling\ urinary\ catheter\ days} \times 1000$$

- **VAP rate per 1000 ventilator/days**

The following formula must be considered:

$$VAP\ rate\ per\ 1000\ ventilator/days = \frac{Number\ of\ VAPs\ infections}{Number\ of\ ventilator\ days} \times 1000$$

- **Treatment**

A dichotomous variable will be calculated for CLABSI infections time period assessment.

Scrub-the-hub protocol – CLABSI infections detected during the first 6 months, pre-intervention period (retrospective period).

Disinfecting barrier cap – CLABSI infections detected during the last 6 months, post-intervention period (prospective period).

- **Compliance by format of disinfecting cap**

Compliance of disinfecting cap strips will be calculated using the previous formula "*Compliance rate for use of the disinfecting barrier cap on needleless connectors (post-intervention period)*" just with the ICU unit data.

Compliance of individual disinfecting cap will be calculated using the previous formula "*Compliance rate for use of the disinfecting barrier cap on needleless connectors (post-intervention period)*" using data of the following unit wards: 2º floor, 3º floor, 3º floor – surgical ward, 4º floor and 5º floor.

10 APPENDIX

External document: CUROS TLFs Version No. 2.0, 03Apr2019