A Randomized Perspective, Open and Parallel Controlled Study Comparing 3M Tegaderm CHG I.V. Securement Dressing with 3M Tegaderm transparent dressing for Evaluation of Antimicrobial Efficacy on Deep Venous Catheters (DVC) Insertion Site in Adult in Critical Care

Study protocol number/version number: EM-05-014894 V1.0

Version date of study protocol: 2020.8.25

Sponsor: 3M China

NCT#: NCT04906512

Statistical analysis plan

(Version: Final draft 1.0)

Author: _ _ _ _ _ _ _ _ _ _ _ _ _ Date: _ _ _ _ _ _ _

Yanrong Zhang, Statistician, GCP(Beijing) ClinPlus Co.,Ltd

Reviewed by: _ _ _ _ _ _ _ _ _ _ _ _ _ Date: _ _ _ _ _ _ _

Liu Wangjun, Senior Statistician, GCP(Beijing) ClinPlus Co.,Ltd

Reviewed by: _ _ _ _ _ _ _ _ _ _ _ _ _ Date: _ _ _ _ _

Yang Ye, Clinical Project Manager, 3M China

Content

1. ABBREVIATIONS AND STATISTICS USED IN THIS ARTICLE 3
2. OBJECTIVES OF THE STUDY 3
2.1 PRIMARY OBJECTIVE 3
2.2 SECONDARY OBJECTIVE 3
3. STUDY DESIGN 4
3.1 OVERALL DESIGN DESCRIPTION 4
3.2 STUDY POPULATION AND SAMPLE SIZE 4
3.3 RANDOMIZATION 4
3.4 STUDY DURATION 4
4. EVALUATION INDICATORS 6
4.1 EFFICACY EVALUATION INDICATORS 6
4.1.1 Major efficacy indictors 6
4.1.2 Secondary efficacy indicator 7
4.2 SAFETY INDICATORS 7
5. STATISTICAL ANALYSIS DATASETS 7
5.1 FULL ANALYSIS SET (FAS) 7
5.2 PER-PROTOCOL SET (PPS) 8
5.3 SAFETY SET (SS) 8
6. STATISTICAL ANALYSIS METHODS 8
6.1 GENERAL PRINCIPLES 8
6.2 DEMOGRAPHICS AND SUBJECT CHARACTERISTICS 9
6.2.1 Completion of enrollment 9
6.2.2 General Information 9
6.2.3 Exposure 10
6.2.3.1 Studied products 10
6.2.3.2 Pre-treatment and combined medication/treatment 10
6.3 EFFICACY EVALUATION 11
6.3.1 Primary Efficacy Evaluation 11
6.3.2 Secondary Efficacy Evaluation 11
6.4 SAFETY EVALUATION 13
7. DATA PROCESSING AND CONVERSION 14
7.1 MISSING SEVERITY OF ADVERSE EVENTS 14
7.2 MISSING RELATIONSHIP BETWEEN ADVERSE EVENTS AND DEVICE 14
7.3 MISSING PRIMARY EFFICACY ENDPOINT 14
8. INTERIM ANALYSIS 14
9. DESCRIPTION ABOUT THE PLAN 15

1. ABBREVIATIONS AND STATISTICS USED IN THIS ARTICLE

Abbreviations	Explanations in details
AE	Adverse Event
ADE	Adverse Device Event
CHG	chlorhexidine gluconate
CI	Confidence Interval
CLABSI	CLABSI infection
CRF	Case Report Form
CRBSI	Catheter-Associated Bloodstream Infection
CVC	Central venous catheter
DD	Device Defect
DVC	Deep venous catheterization
FAS	Full Analysis Set
ITT	Intention to Treat
Max	Maximum
Mean	Means
Min	Minimum
PICCO	Pulse indicate Contour Cardiac Output
SAE	Serious Adverse Event
SADE	Serious Adverse Device Event
SAP	Statistical Analysis Plan
SAR	Statistical Analysis Report
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operation Procedure
SS	Safety Set
USADE	Unexpected Serious Adverse Device Event

2. OBJECTIVES OF THE STUDY

2.1 Primary objective

The primary objective of this study is to compare the difference in the bacterial colonization rate at CVC tips and catheter sites on the skin after removal (number of culture-positive cases/total catheters × 100%) between the test and control groups.

2.2 Secondary objective

The secondary objective of this study is to compare the differences in the following indicators between the test and control groups:

• Number of positive cases per 1,000 catheter-days of bacterial colonization at CVC tips

• Bacterial colonization rate at the tip of other types of (percutaneous) deep vein catheters and the catheterization site (number of culture positive cases/total catheters x 100% and number of positive cases per 1,000 catheter-days), including hemodialysis, PICCO, float catheters, etc.

• Incidence rate of Central Line Associated Bloodstream Infections (CLABSI) or Catheter Related Blood Stream Infections (CRBSI)

• Type of pathogenic microorganism (G+/G-/fungal or specific species, drug-resistant bacteria, etc.) and percentage of positivity

• Securement performance of the dressing: Frequency of dressing changes associated with wearing time and warping or peeling

• Effects on the skin of the covered area, e.g. local infection, local skin irritation

3. STUDY DESIGN

3.1 Overall Design Description

This clinical trial is designed as a prospective, randomized, open-label, parallel-group controlled trial.

3.2 Study Population and Sample Size

440 subjects who meet the inclusion/exclusion criteria will be enrolled. Subjects will be adult voluntary clinical subjects, of either sex, at least 18 years of age, who are ICU patients undergoing deep venous catheterization (DVC), in which a CVC catheter must be used while other types of catheters such as hemodialysis, PICCO,and floating catheters may be used concurrently.

This study will use a positive two-sided Z test for continuity calibration and use the O'Brien-Fleming expenditure function to determine the test boundary. Assuming a baseline value of 18.7% for CVC tips colonization rate in the control group (this figure is reported by a domestic epidemiological survey) and a reduction rate of 50.0%, each group should contain at least 220 patients with CVC to reach an 80% likelihood at 5% significance level. A total of 440 valid cases are required in both groups combined. An interim analysis is scheduled for this study and will be conducted after completion of follow-up visits of 220 subjects to correct for the pre-defined sample size.

3.3 Randomization

After investigators confirm checks of inclusion and exclusion criteria, eligible participants were given a randomization number through the online randomization service system and randomly assigned to either the trial or control group to receive trial treatment in a 1:1 grouping ratio. The random number table was generated by a biostatistician using a program prior to enrollment of the first participant and then imported into the online randomization service system. See the randomization scheme for details.

3.4 Study Duration

The duration of the study is expected to be 15 months, from enrollment of the first subject to departure of the last subject.

Depending on the subject's disease treatment schedule, each study subject would be treated with the same deep vein placement for essentially no more than 2 weeks, so their participation in the study would last for approximately 3-14 days.

Table 3.1 Schedule of events

Process	Screening and enrollment Day 0	Dressing change visits	Treatment end Visit	Withdrawal or discontinuance of visits
Informed consent form	X			
Assessment of inclusion/exclusion criteria	X			
Randomization	X			
Demographic	X			
Previous medical history	X			
Vital signs	X		X	X
Blood routine test	X		X	X
Record of deep vein catheterization	X		X	X
Skin assessment around the catheter site	X	X	X	X
Dressing application or change (multiple times)	X	X		
Documentation of relevant concomitant medication	X	X	X	X
Evaluation of subject product (dressing edge curling, etc.)		X	X	X
Total duration of catheterization			X	
Total duration of test/control dressing use			X	
Catheter-tip bacterial culture			X	
Bacterial culture from skin samples around the insertion site			X	
Blood bacteriological culture			X	
AE/SAE	X	X	X	X
Device Defect	X	X	X	X

4. EVALUATION INDICATORS

4.1 Efficacy evaluation indicators

4.1.1 Major efficacy indictors

（1） Occurrence rate of bacterial colonization of the CVC tip segment and skin at the insertion site after extubation (number of culture-positive cases/total number of catheters × 100%).

The primary endpoint is the removal of the CVC from the patient with deep vein catheterization to perform catheter-tip culture and sampling and culture of bacteria from the skin around the insertion site

4.1.2 Secondary efficacy indicator

（1） Number of positive cases per 1,000 catheter-days of bacterial colonization at the tip of the CVC (number of culture-positive catheters/total catheter retention time (days) * 1000%));

（2） Bacterial colonization rate at the tip of other types of (percutaneous) deep vein catheters and the catheterization site (number of culture positive cases/total catheters x 100% and number of positive cases per 1,000 catheter-days), including hemodialysis, PICCO, float catheters, etc;

（3） Occurrence of suspected CLABSI/CRBSI, which entails catheter tip bacterial culture and blood bacterial culture

（4） Securement performance of the dressing: Frequency of dressing changes associated with wearing time and warping or peeling

participant wear time (hours) = sum of all dressing wear times (hours) for the participant/participant dressing changes
Number, where wear time (hours) for each dressing = change date time - use date time.

Replacement due to edge lifting and droping out is defined as whenever there is a dressing replacement due to edge lifting and droping out, it is determined that the participant
appears to be replaced.

4.2 Safety indicators

（1） Adverse events;

（2） Vital signs: Including temperature, respiration, pulse, systolic blood pressure, diastolic blood pressure, and study time point: Screening and enrollment, withdrawal/discontinuation of visits or end-of-treatment visits.

（3） Laboratory Check: Blood routine includes red blood cell count, white blood cell count, platelet count, neutrophil %, neutrophil count, lymphocyte %, lymphocyte count, hemoglobin, C-reactive protein, and study time point: Screening and enrollment, withdrawal/discontinuation of visits or end-of-treatment visits.

（4） Effects on the skin of the covered area, e.g. local infection, local skin irritation

5. STATISTICAL ANALYSIS DATASETS

5.1 Full Analysis Set (FAS)

The set of subjects determined according to the principle of Intention To Treat (ITT) refers to the data set composed by all subjects who are involved in the trial randomly and have used the trial product. The missing data were carried forward using the strategy of

WCCF (Worst Case Care Forward) in case the primary efficacy endpoints of the patients were not observed.

FAS is the primary analytical data set for evaluating validity. In addition, FAS will be used for drop-out analysis, and equilibrium analysis of basic index.

5.2 Per-Protocol Set (PPS)

PPS is a subset of the FAS and includes subjects randomly assigned to treatment with a test or control device who have not experienced significant protocol deviations. The PPS is the secondary analytical data set for evaluating validity.

5.3 Safety Set (SS)

This includes all subjects who have been formally enrolled and completed catheterization and dressing securement with the catheter in place for more than 24 hours.

This data set is used to evaluate the safety of this trial.

6. STATISTICAL ANALYSIS METHODS

6.1 General Principles

Statistical analyses will be performed using SAS 9.4.

In accordance with the O'Brien-Fleming expenditure function, all statistical tests in the final analysis were two-sided, and a p-value of less than 0.048 would be considered statistically significant for the difference being tested (except where specially described).

The description of quantitative indicators will calculate the number of cases (missing), mean, standard deviation, median, minimum, and maximum. The minimum and maximum values will have the same decimal digits retained as the raw data, but the mean, standard deviation, and median will have one more decimal digits than the raw data. However, generally the maximum number of raw data will not exceed four decimals.

The description of qualitative indicators will use the number of cases and percentages of each category. Calculation of percentage was based on non-missing data in the analysis set. Percentage was rounded to one decimal number. Unless special instruction, percentages will be calculated using the number of people in the corresponding group for each population as the denominator.

All numerically derived variables will keep two decimals, unless otherwise specified.

The treatment of missing data will be described in a separate section, otherwise all missing data will not be filled.

Missing days in the date will be filled using 1 day, and missing months will be filled using 1 month, as a general principle for filling missing dates, unless special instruction.

Baseline will be defined as the last test value prior to treatment.

Change relative to baseline in this paper will be defined as post-treatment minus baseline.

6.2 Demographics and Subject Characteristics

6.2.1 Completion of enrollment

Summarize all screenings and the number of failed screenings. Summarize the number and proportion of participant in the randomized population who used the investigational product by randomization, who did not use the investigational product by randomization, who did not use the investigational product, who completed the trial, and who did not complete the trial; the number and proportion of participant who did not complete the trial will be summarized in detail with the reasons for withdrawal from the trial on the trial summary page.

List participants in the randomized population who did not complete the trial in detail. List participants who did not enter the PPS (with reasons for scheme violation) in detail.

6.2.2 General Information

（1） Evaluation Indicators

1) Demographic information: Age, gender, nationality, height and weight;
2) General Condition: medical history, allergic history.
3) Deep vein indwelling catheterization and peripheral skin evaluation status: Insertion site, insertion type, duration of insertion (days), with or without blood oozing after puncture placement, whether other products were applied, whether emergency insertion was performed, whether skin assessment around the insertion site was performed, skin assessment around the insertion site (including erythema, edema, pruritus score and whether skin infection was diagnosed);

✧ Methodology for calculating relevant indicators:

- ✓ Age (years) = (date of informed consent - date of birth + 1) / 365.25, rouding to whole numbers
- ✓ Duration of tube insertion (days) = date of randomization - date of tube insertion + 1

（2） Evaluation method

FAS was used for evaluation.

The demographic data, general conditions were described accordingly to their numerical characteristics and quantitative indicators were compared between the two groups of participants using t-test/Wilcoxon rank sum test; qualitative indicators were compared between the two groups of participants using chi-square test/Fisher exact

probability method.

Summary of the evaluation of deep vein indwelling catheterization and surrounding skin at the level of the insertion site. The two groups of quantitative indicators were compared using t-test/Wilcoxon rank sum test according to their corresponding numerical characteristics description; and the two groups of qualitative indicators were compared using chi-square test/Fisher exact probability method.

In addition, a list of data on medical history, allergic history, deep vein indwelling catheterization prior to enrollment and skin evaluation around the insertion site, and previous/concomitant medication was made for both groups of participants.

6.2.3 Exposure

6.2.3.1 Studied products

Quantitative descriptive statistics (number of cases, mean, standard deviation, median, minimum, maximum) were used to describe the study time (days) for both groups of participants. Quantitative descriptive statistics (number of cases, mean, standard deviation, median, minimum, maximum) were used to describe the total insertion time (h) and total dressing using time (h) for the two groups with different DVC catheters, respectively.

- Duration of study: Study duration is from the date of randomization to the date of completion/withdrawal from the trial when participants were studied on the study summary page.
  - ✓ *Study Duration (days) = date of completion/withdrawal from trial - date of randomization + 1*

6.2.3.2 Pre-treatment and combined medication/treatment

Pre-treatment and combined medications were coded according to the classification of the Dictionary of Contemporary Drug Trade Names and Aliases (organized and edited by the Chinese Pharmaceutical Association, published and distributed by Chemical Industry Press and Modern Biotechnology and Pharmaceutical Technology Publishing Center, 2nd edition, August 2006). Pre-treatment medication is defined as medication prior to the first application of any investigational product. Combined medication was defined as any medication at and after the first application of investigational product. Pre-treatment and combined medications were summarized for each group according to the coded systemic and canonical names, and the number of cases, percentage, and case times were calculated. Details of pre-treatment and combined medications are given in list form.

Pre-treatment and combined treatments were coded according to the latest edition of the Medical Dictionary for Regulatory Activitie (MedDRA) classification. Pre-treatment

is defined as treatment prior to the first application of any investigational product. Combination treatment was defined as any treatment at and after the first application of investigational product. The groups were summarized by system organ classification (SOC) and preferred terminology (PT), and the number of cases, percentage, and case times were calculated. Details of pre-treatment and combined treatment are given in list form.

6.3 Efficacy Evaluation

6.3.1 Primary Efficacy Evaluation

（1） Evaluation Indicators

Occurrence rate of bacterial colonization of the CVC tip segment and skin at the insertion site after extubation (number of culture-positive cases/total catheters × 100%)

Primary endpoint: Positive rates of catheter tip cultures and sampling cultures of skin surrouding the insertion site in patients with deep vein indwelling catheterization after CVC tubes were removed.

（2） Evaluation method

FAS and PPS were used for both total catheter count and participant level evaluation. If more than one catheter of the same type was available for the same participant and the culture results were inconsistent, a positive culture result was taken for that participant when participant-level analysis was performed.

Describe the number and percentage of cases of bacterial colonization of the CVC tip segment and skin at the insertion site after extubation in both groups, and compare the two groups using a chi-square test or Fisher's exact test.

In addition, because some subject may have two or more than two CVC, which are interrelated, a generalized mixed linear model was developed to evaluate the difference in the occurrence rate of bacterial colonization between the two groups, using the occurrence rate of bacterial colonization of the CVC tip segment after extubation and the occurrence rate of bacterial colonization of the skin at the CVC insertion site after extubation as dependent variables, group as a fixed effect, and insertion site, skin infection of baseline insertion site, and their interaction as random effects, respectively.

6.3.2 Secondary Efficacy Evaluation

（1） Evaluation Indicators

1) Number of positive cases per 1,000 catheter-days of bacterial colonization at CVC tips;
2) Bacterial colonization rate at the tip of other types of (percutaneous) deep vein

catheters and the catheterization site (number of culture positive cases/total catheters x 100% and number of positive cases per 1,000 catheter-days), including hemodialysis, PICCO, float catheters, etc;

3) Occurrence of suspected CLABSI/CRBSI, which entails catheter tip bacterial culture and blood bacterial culture
4) Securement performance of the dressing: Frequency of dressing changes associated with wearing time and warping or peeling

（2） Evaluation method

FAS and PPS were used for evaluation.

Quantitative descriptive statistics (number of cases, mean, standard deviation, median, minimum, maximum) were used to describe the number of positive cases per 1,000 catheter-days occurring in the two groups of CVC tip bacterial colonization, and t-test or rank sum test was used to compare the two groups. In addition, a mixed linear model was developed to evaluate the difference in the number of positive cases per 1,000 catheter days of bacterial colonization between the two groups, using the number of positive cases per 1,000 catheter days of bacterial colonization of the CVC tip segment after extubation as the dependent variable, group as a fixed effect, and insertion site, skin infection of baseline at the insertion site, and their interaction as random effects.

The number and percentage of cases of bacterial colonization at the tip of other types of (percutaneous) deep vein catheters and the catheterization site after extubation were described separately for both groups with the total number of catheters and at the participant level, and the two groups were compared using the chi-square test or Fisher's exact test.

Quantitative descriptive statistics (number of cases, mean, standard deviation, median, minimum, maximum) were used to describe the number of positive cases per 1,000 catheter days occurring at the tip of other types of (percutaneous) deep vein catheters and the catheterization site after extubation in both groups. If more than one catheter of the same type was placed in the same participant, it will be analyzed with the total number of catheters and participant level separately and the two groups will be compared using a t-test or Wilcoxon rank sum test.

The number of cases, case times and occurrence rate of suspected CLABSI/CRBSI occurred in the two groups of different bacteriological culture specimens types and at catheter locations were calculated, and the two groups were compared using the chi-square test or Fisher's exact test.

The number of cases, case times and occurrence rate of positive occurrences in the two groups of different bacteriological culture specimens types were summarized by bacterial classification, specific bacterial name, and the two groups were compared using the chi-square test or Fisher's exact test, respectively.

Quantitative descriptive statistics (number of cases, mean, standard deviation, median, minimum, maximum) were used to describe the duration of dressing wear in both groups and t-test or rank sum test was used to compare the two groups. The frequency of dressing changes due to edge lifting and droping out was described for both groups of participants and the two groups were compared using the chi-square test or Fisher's exact test.

6.4 Safety Evaluation

（1） Evaluation Indicators

1) Adverse events;
2) Vital signs: including temperature, respiration, pulse, systolic blood pressure, diastolic blood pressure;
3) Laboratory Check: Blood routine:
4) Effects on the skin of the covered area, e.g. local infection, local skin irritation.

（2） Evaluation method

Safety analysis was performed using the safety analysis population (SS).

The adverse event was coded according to the latest edition of the Medical Dictionary for Regulatory Activitie (MedDRA). Adverse events that occurred prior to randomization will be listed in the list only.

The analysis of AE will be based on Treatment Emergent Adverse Event (TEAE) during the treatment period. Any AE after the first application of the investigational device, whether or not related to the investigational device, will be defined as a TEAE, as will an AE that existed prior to the application of the investigational device but that worsens during the treatment period. In cases where AE cannot be defined as occurring before the first application of the investigational device or after the first application of the investigational device, AE will be classified as occurring after the first application of the investigational device as the most conservative approach.

The number of cases, case times, and percentages of all TEAEs, TEAEs belonging to CLABSI, TEAEs belonging to CRBSI, and TEAEs occurring in association with the investigational device are tabulated and summarized by system organ (SOC), preferred term (PT), and severity, respectively, for each group. Multiple occurrences of the same adverse event in the same participant will be summarized using the most severe one for severity and relevance to the investigational device.

TEAEs leading to study discontinuation, serious adverse events, and adverse events leading to death were summarized for each group by system organ (SOC), preferred term (PT), respectively, in descending order of the number of cases occurring in the test group.

Adverse events associated with the investigational device included a relationship to the investigational device determined to be: "relevant", "may be relevant".

Adverse events that led to study discontinuation included the choice of measures taken for the investigational device as: "Permanent deactivation of the investigational device".

All adverse events during the study, adverse events leading to study discontinuation, adverse events leading to death and serious adverse events will be detailed in the list.

Describe separately vital signs and baseline variation at the baseline and the last (i.e., end of treatment or withdrawal from discontinuation visit) visit and compare the two groups with t-test.

All tests completed at the last visit and descriptive statistics were listed for laboratory examination in the form of a pre- and post-treatment cross-tabulation (normal/abnormal results determined according to the range of normal values). A list of laboratory examination that appear abnormal after treatment, including random number, treatment group, test time point, item, measured value, and normal value range.

Qualitative descriptive statistics were used to describe separately erythema, erythema, pruritus score and skin infection at the baseline and last (i.e., end of treatment or withdrawal discontinuation visit) visit at different insertion sites in two groups and compare the two groups using the chi-square test or Fisher's exact test.

7. DATA PROCESSING AND CONVERSION

7.1 Missing severity of adverse events

Missing severity of adverse events before randomization will be filled using "moderate". Missing severity of adverse events that occur after randomization will be filled using "severe" and these filled values will be used for occurrence rate summaries only and will be presented as original values in the final list.

7.2 Missing relationship between adverse events and device

Missing relationship between adverse events occurring after randomization and investigational device will be filled in using "relevant", and these filled-in values will be used for occurrence rate summary only and will be presented as original values in the final list.

7.3 Missing primary efficacy endpoint

Missing primary efficacy endpoint will be filled using the WCCF (i.e., filled as "positive"), while, at the same time, giving the result of not filling.

8. INTERIM ANALYSIS

The interim analysis will be performed when enrollment reaches 220 participants, and this interim analysis will be performed by an unblinded team (including statisticians

and programmers) to recalculate the total sample size needed to adjust this study based on the results of the primary endpoint of 220 participants already enrolled and the dropout rate. If the results of the interim analysis show that: When the difference of the primary endpoint between the two dressings, i.e., the positive rate of bacterial culture of the CVC tip segment and skin at the insertion site (either one), is greater than 50% and the p-value is less than 0.005, and with all other considerations to support the objectives and the assumptions of the study were met, the study will be discontinued early with a final statistical analysis report. Otherwise, only issue: The decision to continue as per the protocol or to increase the sample size at a later stage; meanwhile, specific analytical findings were maintained blinded until the entire study was unblinded for final analysis. If the sample size recalculated for the interim analysis was less than or equal to that specified in the protocol, the final analysis was performed when the subsequent test was conducted to the sample size specified in the protocol; if the sample size recalculated for the interim analysis exceeded that specified in the protocol, the final analysis was performed when the subsequent test was conducted to the re-estimated sample size.

In accordance with the O'Brien-Fleming expenditure function, all statistical tests for this interim analysis were two-sided, and p-values less than 0.005 were considered statistically significant for the differences tested.

9. DESCRIPTION ABOUT THE PLAN

<This Statistical Analysis Plan (SAP) provides a more technical and detailed description of the efficacy and security index than the study protocol (version v1.0, dated 2020.8.25>) and proposes specific statistical analysis methods for the relevant evaluation indicators, taking into account the numerical characteristics of the indicators in the study protocol and the specific requirements of this study. The tables, graphs, and lists associated with this plan will be provided in a separate, unique file.