CONFIDENTIAL STATISTICAL ANALYSIS PLAN

A Prospective Randomized Controlled Study Evaluating the Safety and Efficacy of EVICEL® Used for Suture-Line Sealing in Dura-Mater Closure During Paediatric Neurosurgical Cranial Procedures

Version: FINAL Date: February 23, 2017

Protocol Number: BIOS-13-006 (Admin. Change 3, dated January 9, 2017)

AUTHENTICATION

The contents of this statistical analysis plan (SAP) adhere to current regulatory guidelines[1,2]. We the undersigned declare that to the best of our knowledge this study will be reported and analysed in accordance with the following SAP.

TABLE OF CONTENTS

CHANGES MADE FROM FINAL VERSION

Not applicable.

1. STUDY OBJECTIVES

The objective of this study is to evaluate the safety and efficacy of EVICEL® (EVICEL) when used for suture-line sealing in dura-mater closure in elective or urgent paediatric cranial neurosurgery to provide intraoperative watertight closure.

2. STUDY DESIGN

This is a prospective, randomized, open-label, multi-center controlled study evaluating the safety and effectiveness of EVICEL as an adjunct to sutured dural closure compared to standard adjunctive dural closure techniques using additional repair sutures only to obtain an intraoperative watertight dural closure. Subjects will be screened and selected from the patient population of approximately 4-8 clinical sites.

Subjects will undergo an elective or urgent posterior fossa or supratentorial procedure (craniectomy or craniotomy). Upon completion of the primary sutured dural repair, the closure will be evaluated for intraoperative CSF leakage with a baseline Valsalva maneuver 20-25 cm H_2O for 5-10 seconds. If a spontaneous leak is apparent immediately after dural closure, no Valsalva will be performed. Subjects who have an identified CSF leak (spontaneous or as identified with the Valsalva) will be enrolled into the study.

A number of 42 paediatric subjects with intra-operative cerebrospinal fluid (CSF) leak following primary suturing of the dura will be randomized to either EVICEL Fibrin Sealant (Human) or to adjunctive dural closure techniques using Additional Sutures only (Control) in a 2:1 allocation ratio and will be stratified by surgical procedure, posterior fossa or supratentorial.

Randomization will be used to avoid bias in the assignment of treatment to each subject, to increase the likelihood that attributes of the subject are balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

ETHICON will provide each site with computer-generated randomization envelopes, each bearing the subject randomization number, and containing the treatment allocation. Treatment will be assigned randomly to each subject on a 2:1 basis to either EVICEL or additional adjunctive repair sutures only. In the event that a potential subject fails intraoperative criteria, and is not randomized to the study, the unused randomization envelope should be returned to the series, and used for the next subject. Given the difference between the two treatment groups, it will not be possible for the surgeon to be blinded to the treatment. However, to avoid any bias in the conduct of the surgical procedure, randomization should only take place after sutured dural closure and the detection of CSF leakage.

Subjects will be followed post-operatively through discharge and for 30 days (±3) post-surgery. The incidence of CSF leaks will be assessed within 5 days (±2 days) and 30 days (±3 days) post-operatively as detected by any of the following: clinical observation, diagnostic testing or the need for surgical intervention to treat a CSF leak or pseudomeningocele.

3. STUDY ENDPOINTS

The **primary** effectiveness endpoint is the proportion of success (intraoperative watertight closure) in the treatment of intraoperative CSF leakage defined as no CSF leakage from dural repair intraoperatively, during a Valsalva maneuver 20-25 cm H_2O for 5-10 seconds.

For subjects randomized to EVICEL, if a CSF leakage is still apparent after the first EVICEL application, a second treatment (up to two layers) with EVICEL may be applied. The CSF leakage will be re-evaluated with the Valsalva maneuver 20-25 cm H_2O for 5-10 seconds. If watertight closure is not evident after this second Valsalva maneuver, the subject will be deemed a failure and the surgeon may revert to his/her standard of care for closure including the use of other commercially available fibrin sealants (except EVICEL®) or an dural patch. If watertight closure is achieved with EVICEL, no additional adjunct should be used and the subject will be deemed a treatment success.

Subjects randomized to control will receive additional dural sutures as deemed necessary by the surgeon. The CSF leakage will be evaluated with the Valsalva maneuver 20-25 cm H_2O for 5-10 seconds. If watertight closure is not evident after the Valsalva maneuver, the subject will be deemed a failure and the surgeon may revert to his/her standard of care for closure including the use of other commercially available fibrin sealants (except EVICEL) or an dural patch. If watertight closure is achieved, but the surgeon feels that an adjunct (excluding the use of fibrin sealants) is required to assure durability of closure, then such treatment should be applied. This will be considered a treatment success.

In addition, the following **safety/secondary** endpoints will be included in this study:

- Incidence of CSF leakage within 5 days (± 2 days) post-operatively;
- Incidence of CSF leakage within 30 days (± 3 days) post operatively;

  The CSF leaks within 5 days (±2 days) and 30 days (±3 days) post-operatively will be detected by any of the following: clinical observation, diagnostic testing or the need for surgical intervention to treat a CSF leak or pseudomeningocele.
- Incidence of adverse events, collected from time of randomization, throughout the follow-up period until 30 days (±3 days) after the procedure;
- Incidence of surgical site infections (SSI) according to National Healthcare Safety Network (NHSN) criteria within 30 days (± 3 days) post-operatively;
- Laboratory tests (complete blood count with differential, liver function tests and electrolytes) at baseline and 5-day (±2 days) visit.

4. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

Not applicable.

5. ANALYSIS SETS

The following three analysis sets defined:

- The Safety set consists of all subjects who received treatment;

- The Full Analysis Set (FAS) consists of all randomized subjects (equivalent to the Intent-to-Treat [ITT] set).
- The Per-Protocol (PP) set consists of all FAS subjects who have no major protocol deviations.

Major protocol deviations are deviations that have an impact on the primary endpoint, or that have an impact on the randomization assignment. These will be determined prior to database lock.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

6.1 Demographic and other baseline characteristics

Demographic and other baseline data will be summarized descriptively for subjects in each treatment group in the FAS set. The categorical data will be summarized descriptively by frequencies along with the associated percentages. The continuous data will be presented using summary statistics such as number of subjects, mean, standard deviation, minimum, median and maximum.

The following demographic variables will be summarized:

- Age;
- Gender;
- Race/ethnicity;
- Height;
- Weight;
- Body mass index;
- Indication of subject being of child bearing age;
- History of SVT, DVT/PE;
- Family history of DVT/PE;
- History of alcohol abuse;
- Smoking status.

In addition, the following screening and baseline data will be collected:

- Physical examination, including documentation of relevant medical and surgical history;
- Complete blood count (CBC) with white blood cell differential, liver function tests and electrolytes;
- Documentation of medical history including all concomitant medications during 24 hours prior to surgery;
- Review of inclusion / exclusion criteria to confirm subject eligibility.

7. PROCEDURE DATA

Procedure data will be summarized descriptively for subjects in each treatment group in the FAS set to assess comparability of treatment groups. The categorical data will be summarized descriptively by frequencies along with the associated percentages. The continuous data will be presented using summary statistics such as number of subjects, mean, standard deviation, minimum, median and maximum.

The following procedure variables will be analyzed:

- Operative procedure, including type of approach, indication for surgery and tumor location, if applicable;
- Operating room (OR) time;
- Procedure duration (from first incision to closure completion);
- Specification of treatment to which subject is randomized;
- CSF leak determination;
- For patients treated with EVICEL, the following data will be analyzed for first EVICEL application and second treatment of EVICEL (if applicable): method of EVICEL application, number of layers applied, indication of spontaneous leak observation, indication of Valsalva maneuver performed after randomized treatment application (if applicable), indication of CSF leak detection after Valsalva, definition of leak (if applicable), and type of tip used.
- EVICEL application summary data, such as total number of kits used, approximate total amount of EVICEL used, derived volume per kit, and indication of watertight closure observed;
- For patients treated with Additional Sutures, number of sutures applied, indication of spontaneous leak observation, indication of Valsalva maneuver performed after randomized treatment application (if applicable), indication of watertight closure observed, and indication of additional treatment required for durability of the dura closure (suture, collagen, oxidized regenerated cellulose and/or other treatment);
- Indication and specification of standard of care method for rescue therapy applied, such as DuraSeal, BioGlue, other glues, hemostasic matrices, autologous and biologic dural patches;
- Length of subject hospital stay (from hospital admission to hospital discharge, as well as from procedure to hospital discharge).

8. EFFECTIVENESS

8.1 General methods of analysis

The Clinical Data Management and Biostatistics groups within Clinical Development at ETHICON will be responsible for the overall analysis of data from this protocol. All analyses/summaries will be produced using SAS® (Version 9.1 (EG) or later).

Data will be summarized descriptively for subjects in each treatment group in the FAS set. The categorical data will be summarized descriptively by frequencies along with the associated percentages. The continuous data will be presented using summary statistics such as number of subjects, mean, standard deviation, minimum, median and maximum.

8.2 Primary effectiveness analysis

The primary effectiveness endpoint is the proportion of success (intraoperative watertight closure) in the treatment of intraoperative CSF leakage defined as no CSF leakage from dural repair intraoperatively, during a Valsalva maneuver 20-25 cm H_2O for 5-10 seconds.

No formal sample size calculation has been performed for this study. The sample size required for the trial is 42 randomized paediatrics subjects recruited from 6-8 sites within the European Union. This sample size is considered adequate by EMA Paediatric Investigation Plan to summarize the data descriptively.

The primary effectiveness endpoint will be analyzed using the FAS and the PP set. However, the primary analysis will be based on the FAS. The PP analysis will be considered confirmatory.

In all cases, treatment allocation will be based on randomization for the primary effectiveness endpoint using the FAS. If more than two subjects are mis-randomized, then an additional confirmatory analysis based on treatment received will be performed for the primary effectiveness endpoint, using the FAS.

The proportion of successes will be summarized descriptively by treatment group. In addition, a two-sided 95% confidence intervals (CIs) will be reported for the ratio of the proportion of success in the EVICEL group/proportion of success in Control group (P_E/P_C), using the Farrington-Manning score method.

8.3 Secondary effectiveness analysis

No secondary effectiveness data will be collected for this study.

8.4 Analysis of follow-up data

The following follow-up data will be summarized descriptively for 5-day (±2 days) and 30-day (±3 days) visits:

- Re-hospitalizations and surgical procedures since previous study visit;
- Relevant changes in medical history and concomitant medications since screening;
- Presence of clinically significant changes to subject since baseline;
- Surgical site assessment, including presence of infection (brain abscess, meningitis, and/or surgical site infection), hematoma (intradural, extradural, and/or subcutaneous), pseudomeningocele, and other surgical site experience;
- Wound healing assessment data;
- CSF leak determination data;
- Laboratory data (complete blood count with differential, creatinine, liver function tests and electrolytes) (for 5-day only).

8.5 Statistical/analytical issues

8.5.1 Handling of dropouts or missing data

For the primary effectiveness endpoint, the analysis for the FAS set will be performed considering missing data as failures; in addition, sensitivity analyses for the FAS set will be performed considering missing data as successes, and, as worst-case, with missing data for the EVICEL group considered as failures and missing data for the Control group considered as successes.

If there are incomplete dates and calculations (e.g. time since procedure) are needed, the following rules are used (no rules will be applied for missing years; this data would normally be expected to be queried):

- Missing date which includes the procedure data: the rules below are followed unless the derived date is pre-procedure, when the derived date will be 1st day after the procedure.

- Missing day: 15th used

8.5.2 Interim analyses and data monitoring

No interim analysis will be performed for this study.

8.5.3 Multiple comparison / multiplicity

Not applicable.

9. SAFETY EVALUATION

9.1 Adverse events

The safety/secondary endpoints listed in section 3 will be summarized using the Safety set.

9.2 Clinical laboratory evaluation

Blood samples will be taken for Complete Blood Count (CBC) with differential, creatinine, liver tests and electrolytes at baseline and at 5 day (± 2 days) visit.

9.3 Vital signs, physical findings and other observations related to safety

Vital signs will not be collected in this study. A physical exam will be performed and medical/surgical history data will be collected at screening. In addition, a physical exam will be performed at 5 day (± 2 days) and 30-day (± 2 days) visits.

9.4 Methods of analysis

All safety/secondary variables will be summarized descriptively only, for Safety analysis set. No inferential statistical analysis will be carried out.

Adverse events will be summarized descriptively by the treatment received, using Medical Dictionary for Regulatory Activities (MedDRA) terminology, in SI units. Values and changes from baseline will be listed, but not summarized.

10. DATA PRESENTATION

The report forms part of an integrated clinical study report. The actual numbering of tables, listings and other outputs may change. Numbering is in accordance with ICH guideline E3[2].

10.1 Procedure or treatment labels

The following labels will be used for all output: **EVICEL** and **Control**.

10.2. Tables and figures

Data will be tabulated by treatment group and, if appropriate, by visit. Continuous data summaries will present (unless stated otherwise) number of observations, number of missing observations (if there are any), mean, standard deviation, minimum, median and maximum. Categorical data summaries will present the number of observations and the corresponding percentage. The following tables will be produced:

10.2.1 In-text tables and figures

These will be produced for the main report in conjunction with the medical writer. These will include, but will not be limited to:

No	Title of table/figure	Notes
F1	Subject disposition	Based on Table 14.1.1.4

No	Title of table/figure	Notes
T1	Demographic characteristics – FAS analysis set	Summary of Table 14.1.2.1
T2	Surgical procedure – FAS analysis set	Summary of key items from Tables 14.1.3.1-14.1.3.7
T3	Statistical summary for primary effectiveness endpoint – Per-Protocol and FAS analysis sets (including sensitivity analysis summary)	Summary of Tables 14.2.1.1 and 14.2.1.2
T4	Summary of AEs occurring in >5% of subjects– Safety analysis set	Summary of 14.3.1.3

T=Table F=Figure

10.2.2 Section 14 tables

Shell tables shown in Appendix 1, according to the code in the 'Shell' column. All table numbers will be prefixed with 14.

No	Title of table/figure	Notes	Shell[1]
1.1	Disposition of subjects, analysis sets and protocol deviations		
1.1.1	Disposition of subjects by centre – FAS	Includes number withdrawn – by center	DS
1.1.2	Enrollment by center – FAS	By center	E
1.1.3	Summary of protocol deviations – FAS	Includes both minor and major protocol deviations	PD
1.1.4	Analysis sets – FAS		ST
1.2	Baseline data	Excludes baseline data that is also measured post procedure and/or safety data	
1.2.1	Demographics – FAS	Age, height, weight, BMI – continuous data (c); gender, race, ethnicity, indication of subject being of child bearing age, history of SVT, DVT/PE, family history of DVT/PE, history of alcohol abuse, smoking status – all discrete data (d)	DG
1.2.2	Baseline characteristics – FAS	Presence of relevant history of prior surgery, indication of any relevant changes in medical history between screening and 24 hours before procedure, and confirmation of subject eligibility - all (d)	G1[2]
1.2.3	Physical exam / medical / surgical history – FAS	Includes frequencies	HX
1.3	Operative data		
1.3.1	Pre-operative data – FAS	Operative procedure, type of approach, indication for surgery, and tumor location (if applicable) - all (d)	G2

[1] Shell: Example table from Appendix 1 (Shell tables). Letters refer to standard output, numbers to project specific output.
[2] For Tables G1, G2, G3 notes will indicate if data is continuous or discrete.

No	Title of table/figure	Notes	Shell[1]
1.3.2	Operative data: CSF leak determination and randomization data – FAS	Indication of spontaneous CSF leak observation, indication of Valsalva maneuver performed, indication of CSF leak observed, and specification of treatment to which subject is randomized – all (d)	G2
1.3.3	Operative data: EVICEL application – FAS	For patients treated with EVICEL, the following data will be analyzed for first EVICEL application and second treatment of EVICEL (if applicable): method of EVICEL application, number of layers applied, indication of spontaneous leak observation, indication of Valsalva maneuver performed after randomized treatment application (if applicable), definition of CSF leak observed (if applicable), indication of CSF leak detection after Valsalva (if applicable), definition of leak (if applicable), and type of tip used - all (d)	G2
1.3.4	Operative data: EVICEL application summary – FAS	Total number of EVICEL kits used (both d and c), approximate total amount of EVICEL used (mL) (c), derived volume per kit (mL) (c), and indication of watertight closure observed (d)	G2
1.3.5	Operative data: Additional Sutures treatment details – FAS	For Control patients, number of sutures applied (c), indication of spontaneous leak observation, indication of Valsalva maneuver performed after randomized treatment application (if applicable), indication of watertight closure observed, and indication of additional treatment required for durability of the dura closure (any additional treatment, suture, collagen, oxidized regenerated cellulose and/or other treatment) – all (d)	G2
1.3.6	Operative data: Standard of Care methods for rescue therapy – FAS	Indication of DuraSeal use (d), number of DuraSeal 5 mL kits used (both c and d), indication of BioGlue use (d), size of BioGlue kits used (d), indication of other glues use (d), indication of hemostasic matrix use (d), predefined hemostatic matrix size used (d), indication of autologous dural patch used (any location, fascia, pericranium, fat, muscle, other autologous dural patch) (d), and biologic dural patch use (d)	G2
1.3.7	Operative data timings – FAS	Time in operating room (c), length of procedure (from first incision to closure completion) (c)	G2
2	Effectiveness data		
2.1	Primary endpoint: success (no CSF leak intraoperatively during Valsalva maneuver)	Includes sensitivity analyses; Includes two-sided 95% CI for the ratio proportion of successes in EVICEL group/proportion of successes in Control group	
2.1.1	Success (no CSF leak intraoperatively during Valsalva maneuver): primary effectiveness analysis – FAS	Missing data considered as: -Analysis#1 (primary effectiveness analysis): failures (d) Sensitivity analysis - missing data considered as: -Analysis#2: successes (d); -Analysis#3: failures for EVICEL and successes for Control (d)	G2
2.1.2	Success (no CSF leak intraoperatively during Valsalva maneuver): sensitivity analysis – PP set	Discrete data	G2

No	Title of table/figure	Notes	Shell[1]
2.2	Follow-up assessments		
2.2.1	Post-surgery to hospital discharge assessment: length of hospital stay - FAS	Length of subject hospital stay from admission to discharge (days), length of subject hospital stay from procedure to hospital discharge (days) (c)	G2
2.2.2	5-day (±2 days) and 30-day (±3 days) follow-up assessments – FAS	Indication of re-hospitalizations since previous study visit, indication of surgical procedures since previous study visit, indication of relevant changes in medical history since screening, presence of clinically significant changes to subject since baseline, surgical site assessment, including presence of infection (brain abscess, meningitis, and/or surgical site infection – superficial incisional, deep incisional and/or organ-space), hematoma (intradural, extradural, and/or subcutaneous), pseudomeningocele, and other surgical site experience, wound healing assessment, CSF leak determination - all (d)	G2
3	Safety data		
3.1	Adverse Events		
3.1.1	Number of subjects experiencing any during/post treatment AE by category – Safety analysis set		AS
3.1.2	Adverse events (during/post treatment) by subject, MedDRA preferred term and system organ class – Safety analysis set		AM
3.1.3	Summary of during/post treatment adverse events by subject and coded terms, preferred terms occurring in >=5% of subjects – Safety analysis set		AM
3.1.4	Summary of during/post treatment serious adverse events by subject and coded terms – Safety analysis set	Includes adverse events for which the answer for CRF question "Serious?" in the CRF is "Yes"	AM
3.1.5	Summary of during/post treatment surgical procedure related (possibly, definitely) adverse events by subject and coded terms – Safety analysis set	Includes adverse events for which the answer for CRF item "Relationship to surgical procedure" is "Possibly related" or "Related".	AM
3.1.6	Summary of during/post treatment study treatment related (possibly, definitely) adverse events by patient and coded terms – Safety analysis set	Includes adverse events for which the answer for CRF item "Relationship to study treatment" is "Possibly related" or "Related".	AM

No	Title of table/figure	Notes	Shell[1]
3.2	Laboratory data	Reported in SI units	
3.2.1	Laboratory data: Complete Blood Count - Safety analysis set	At baseline and at 5-day follow-up	L
3.2.2	Laboratory data: White Blood Cell Differential - Safety analysis set	At baseline and at 5-day follow-up	L
3.2.3	Laboratory data: Creatinine, Liver Function Test and Electrolytes - Safety analysis set	At baseline and at 5-day follow-up	L
3.3	Other safety data		
3.3	Safety/secondary endpoints – Safety analysis set	Incidence of CSF leakage within 5 days (± 2 days) post-operatively, incidence of CSF leakage within 30 days (± 3 days) post operatively, and incidence of surgical site infections (SSI) according to National Healthcare Safety Network (NHSN) criteria within 30 days (± 3 days) post-operatively (separately for any SSI, superficial incisional SSI, deep incisional SSI, and organ/space SSI) – all (d)	G2

Note: '–' indicates a new line in the title.

10.3 Listings

Listings will be presented in centre, subject and visit order. The listings will be produced using the data from all subjects.

The columns indicate the listings that will be included in the report. All data available on the database, with the exception of fields used for administration, e.g. signature fields, will be included in the listing for the report.

Missing data will be shown by a space.

10.3.1 Appendix 16.2 listings:

All listings will be prefixed with 16.2.

No	Title of listing	Notes	CRF Page
1	Disposition of subjects		
1.1	Disposition of subjects	Includes reason for withdrawal and time to withdrawal	54
1.2	Visit dates	Includes informed consent and discharge details Includes derived data: -Nights in hospital -Days from procedure	Various
2	Protocol deviations		
2	Protocol deviations		50 and 52
3	Subjects excluded from the analysis		
3	Definition of analysis sets	As defined in Section 5 of this SAP	

No	Title of listing	Notes	CRF Page
4	Baseline characteristics		
4.1	Demographics, special histories, smoking status, and subject eligibility		8 and 10
4.2	Physical exam / medical / surgical history		12, 14, and 16
4.3	Inclusion and exclusion criteria		5
4.4	Concomitant medications	Derived data: -Days from procedure to start -Duration of Con Med	46 and 48
5	Surgical details		
5.1	Surgical procedure - re-operative information, timings including operation room and length of procedure, initial CSF leak determination, and randomization data	Includes derived data: -Time in the operating room -Length of procedure	18, 20, and 22
5.2	Surgical procedure – EVICEL application details		24 and 25
5.3	Surgical procedure – EVICEL application summary		25
5.4	Surgical procedure - Additional Sutures treatment details		28
5.5	Surgical procedure – Standard of Care methods for rescue therapy		30 and 31
6	Effectiveness data		
6.1	Effectiveness - primary effectiveness endpoint		
6.1	Primary effectiveness endpoint - Success (no CSF leak preoperatively during Valsalva maneuver) - FAS (sensitivity analysis) and PP set	Includes derived data: For ITT, missing data considered as: -Analysis#1 (primary): failures (d) Sensitivity analysis - missing data considered as: -Analysis#2: successes (d); -Analysis#3: failures for EVICEL and successes for Control (d)	
6.2	Follow-up assessments		
6.2.1	Post-surgery to hospital discharge assessment – length of hospital stay	Includes derived data: -Days from admission to discharge -Days from procedure to discharge	1
6.2.2	5-day (±2 days) and 30-day (±3 days) follow-up assessments		1 and 34
7	Safety data		
7.1	Adverse event listings (each subject)		
7.1.1	Adverse events	Includes derived data: -Days from procedure to start -Duration of AE	40, 42 and 43
7.1.2	Adverse event comments		42

No	Title of listing	Notes	CRF Page
7.1.3	Adverse events (MedDRA codes)		40, 42 and 43
7.1.4	Serious adverse events		40, 42 and 43
7.2	Laboratory data		
7.2.1	Laboratory data - Complete Blood Count	At baseline and at 5-day follow-up	37
7.2.2	Laboratory data - White Blood Cell Differential	At baseline and at 5-day follow-up	37
7.2.3	Laboratory data – Creatinine, Liver Function Tests and Electrolytes	At baseline and at 5-day follow-up	37
7.3	Other safety data		
7.3	Safety/secondary endpoints	Includes derived data: -Incidence of CSF leakage within 5 days (± 2 days) post-operatively -Incidence of CSF leakage within 30 days (± 3 days) post operatively -Incidence of surgical site infections (SSI) according to National Healthcare Safety Network (NHSN) criteria within 30 days (± 3 days) post-operatively (separately for any SSI, superficial incisional SSI, deep incisional SSI, and organ/space SSI)	24, 25, 28, and 34

10.3.2 Data review

Listings will be available for regular listing reviews to be organized by Data Management.

11. REFERENCES

1 ICH harmonised tripartite guideline - Statistical principles for clinical trials (E9) – Step 4, 05 Feb 1998.

2 ICH harmonised tripartite guideline - Structure and contents of clinical study reports (E3) – Step 4, 30 Nov 1995.

APPENDIX 1: TABLE TEMPLATES (SEE ATTACHED DOCUMENT)

APPENDIX 2: CDC/NHSN CRITERIA FOR DEFINING A SURGICAL SITE INFECTION (SSI)

Superficial Incisional SSI

Infections occur within 30 days after the operation *and* infection involves only skin or subcutaneous tissue of the incision *and* at least *one* of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture or fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision is deliberately open by surgeon, *unless* incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Do *not* report the following conditions as SSI:

1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration.
2. Infection of an episiotomy or newborn circumcision site.
3. Infected burn wound.
4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

Note: Specific criteria are used for identifying infected episiotomy and circumcision site and burn wounds.

Deep Incisional SSI

Infections occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves deep soft tissues (e.g., fascial and muscles layers) of the incision *and* at least *one* of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Notes:

1. Report infection that involves both superficial and deep incisional sites as deep incisional SSI.
2. Report organ/space SSI that drains through the incision as a deep incisional SSI.

Organ/space SSI

Infections occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves any part of the anatomy (e.g., organs or spaces) other than the incision, which was opened or manipulated during an operation *and* at least *one* of the following:

1. Purulent drainage from a drain that is placed through a stab wound into the organ space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histological or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

APPENDIX 1 - Notes on Shell Tables

These are meant to represent the **style** of tables, slight differences in the CRF will result in more/less rows in the tables or more/less categories for a parameter. Items to note are highlighted in green.
Single arm studies will only have one column of data (unless specific comparisons detailed in SAP).
Treatment labels will be as defined in section 7.1.
Footnotes will change according to the requirements of the study.

EXAMPLE TABLE AM (Adverse Event MedDRA summary)

Table 14.3.1.x
<<Title as SAP>> ^
Safety analysis set

System organ class	Preferred term	Ethicon trt (n=99)	Comparator (n=99)	Total (n=999)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Total	9 (9.9%)	9 (9.9%)	9 (9.9%)
	ANAEMIA	9 (9.9%)	9 (9.9%)	9 (9.9%)
CARDIAC DISORDERS	Total	9 (9.9%)	9 (99.9%)	99 (9.9%)
	ACUTE MYOCARDIAL INFARCTION	9 (9.9%)	9 (9.9%)	9 (9.9%)
	ANGINA PECTORIS	9 (9.9%)	9 (9.9%)	9 (9.9%)
	ATRIAL FIBRILLATION	9 (9.9%)	9 (9.9%)	9 (9.9%)
	ATRIOVENTRICULAR BLOCK COMPLETE	9 (9.9%)	9 (9.9%)	9 (9.9%)
	CARDIAC ARREST	9 (9.9%)	9 (9.9%)	9 (9.9%)
	CARDIAC FAILURE	9 (9.9%)	9 (9.9%)	9 (9.9%)
	CARDIAC FAILURE CONGESTIVE	9 (9.9%)	9 (9.9%)	9 (9.9%)
	MITRAL VALVE INCOMPETENCE	9 (9.9%)	9 (9.9%)	9 (9.9%)
	MYOCARDIAL INFARCTION	9 (9.9%)	9 (9.9%)	9 (9.9%)
	SINUS BRADYCARDIA	9 (9.9%)	9 (9.9%)	9 (9.9%)
	SUPRAVENTRICULAR TACHYCARDIA	9 (9.9%)	9 (9.9%)	9 (9.9%)
	TACHYCARDIA	9 (9.9%)	9 (9.9%)	9 (9.9%)
	VENTRICULAR TACHYCARDIA	9 (9.9%)	9 (9.9%)	9 (9.9%)
ENDOCRINE DISORDERS	Total	9 (9.9%)	9 (9.9%)	9 (9.9%)
	ADRENAL MASS	9 (9.9%)	9 (9.9%)	9 (9.9%)
GASTROINTESTINAL DISORDERS	Total	99 (99.9%)	99 (99.9%)	99 (99.9%)
	ABDOMINAL DISTENSION	9 (9.9%)	9 (9.9%)	9 (9.9%)
	ABDOMINAL HAEMATOMA	9 (9.9%)	9 (9.9%)	9 (9.9%)
	ABDOMINAL PAIN	9 (9.9%)	9 (9.9%)	9 (9.9%)
	ACUTE ABDOMEN	9 (9.9%)	9 (9.9%)	9 (9.9%)
	CONSTIPATION	9 (9.9%)	9 (9.9%)	9 (9.9%)
	DIARRHOEA	9 (9.9%)	9 (9.9%)	9 (9.9%)
	DYSPEPSIA	9 (9.9%)	9 (9.9%)	9 (9.9%)
	GASTRIC ULCER	9 (9.9%)	9 (9.9%)	9 (9.9%)

[If any Ethicon specific codes used these will be indicated with an '*']
[FIRST PAGE ONLY SHOWN]

EXAMPLE TABLE AS (Adverse Event Overall Summary)

Table 14.3.1.1
Number of patients experiencing any during/post treatment AE by category
Safety analysis set

Variable		Category /Statistic	Ethicon trt (n=99)	Comparitor trt (n=99)	Total (n=999)
Individual AE	(^)	Yes	999 (na)	999 (na)	999 (na)
Individual SAE	(^)	Yes	999 (na)	999 (na)	999 (na)
At least 1	($)	Yes	99 (99.9%)	99 (99.9%)	99 (99.9%)
Serious	($)	Yes	99 (99.9%)	99 (99.9%)	99 (99.9%)
Severe	($)	Yes	99 (99.9%)	99 (99.9%)	99 (99.9%)
Action taken	(%$)	Yes	99 (99.9%)	99 (99.9%)	99 (99.9%)
Related	(+$)	Yes	9 (99.9%)	9 (9.9%)	9 (9.9%)

[Categories as AE page in CRF, definition of '+' as in SAP]

EXAMPLE TABLE DC (Discrete data- change)

Table 14.x.x.x
Xxxxxxxxxxxx
xxxx analysis set

Variable	Category	Baseline Missing	Category 1	Category 1	Category 1	Category 1	TOTAL
Proc, Variable, Visit xx	Missing	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)
	Category 1	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)
	Category 2	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)
	Category 3	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)
	Category 4	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)
	TOTAL	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)	9 (9.9%)
Proc, Variable, Visit xx	Improving^						9 (9.9%)

[Improving should not be given if it is not clear what improvement is.
[For two treatment studies include variable name in the heading, and in the variable column add treatment]

^ percentage is based on those with non-missing values for baseline and visit

EXAMPLE TABLE DG (Demographics)

Table 14.1.2.1
Demographics [or Baseline characteristics for 14.1.2.2]
xxx analysis set

Variable	Category /Statistic	Ethicon trt (n=99)	Comparator trt (n=99)	Total (n=99)
Age (years)	Mean (std)	99.9 (99.9)	99.9 (99.9)	99.9 (99.9)
	Median (range)	99.9 (99.9,99.9)	99.9 (99.9,99.9)	99.9 (99.9,99.9)
	Number (missing)	99 (9)	99 (9)	99 (9)
	95% CI of mean .	99.9 ,99.9	99.9 ,99.9	99.9 ,99.9
Age (years, grouped)	<16	9 (9.9%)	9 (9.9%)	9 (9.9%)
	16-<50	9 (9.9%)	9 (9.9%)	9 (9.9%)
	50-<65	9 (9.9%)	9 (9.9%)	9 (9.9%)
	65+	9 (9.9%)	9 (9.9%)	9 (9.9%)
Height (cm)	Mean (std)	99.9 (9.9)	99.9 (99.9)	99.9 (99.9)
	Median (range)	99.9 (99.9, 99.9)	99.9 (99.9, 99.9)	99.9 (99.9, 99.9)
	Number (missing)	99 (9)	99 (9)	99 (9)
	95% CI of mean .	99.9 , 99.9	99.9 , 99.9	99.9 , 99.9
Weight (kg)	Mean (std)	99.9 (99.9)	99.9 (99.9)	99.9 (99.9)
	Median (range)	99.9 (99.9, 99.9)	99.9 (99.9, 99.9)	99.9 (99.9, 99.9)
	Number (missing)	99 (9)	99 (9)	99 (9)
	95% CI of mean .	99.9 ,99.9	99.9 ,99.9	99.9 ,99.9
BMI (kg/m2)	Mean (std)	99.9 (9.9)	99.9 (9.9)	99.9 (9.9)
	Median (range)	99.9 (99.9,99.9)	99.9 (99.9,99.9)	99.9 (99.9,99.9)
	Number (missing)	99 (9)	99 (9)	99 (9)
	95% CI of mean .	99.9 ,99.9	99.9 ,99.9	99.9 ,99.9
Gender	Male	99 (99.9%)	99 (99.9%)	99 (99.9%)
	Female	99 (99.9%)	99 (99.9%)	99 (99.9%)
Race	Caucasian	99 (99.9%)	99 (99.9%)	99 (99.9%)
	Black	9 (9.9%)	9 (99.9%)	9 (9.9%)
	Asian	9 (9.9%)	9 (9.9%)	9 (9.9%)
	Hispanic	9 (99.9%)	9 (99.9%)	9 (99.9%)

Baseline characteristics table similar- includes items recorded at baseline only that are not demography
[Example layout, Demographics are as CRF, Age groupings as defined in SAP]

Study: [Short title and number]
Program: t_all.sas Run date: 12SEP06 Time: 08:40
CONFIDENTIAL Programmer: << name >> Program status: VALIDATED Data Status: LOCKED ON DDMMM20YY
Source: Listing 16.2.4.1 [or 4.2 for baseline characteristics]
&: of African descent

EXAMPLE TABLE DS (Disposition of subjects)

Table 14.x.x.x
Disposition of subjects by centre
xxx analysis set

Variable		Category /Statistic	Ethicon trt (n=99)	Comparator trt (n=99)	Total (n=99)
Overall		Not withdrawn	99 (99.9%)	99 (99.9%)	99 (99.9%)
		Other	9 (9.9%)	9 (9.9%)	9 (9.9%)
Town	Country	Not withdrawn	9 (99.9%)	9 (99.9%)	9 (99.9%)
		Other	9 (9.9%)	9 (9.9%)	9 (9.9%)

[Similar for all other centres]
[Withdrawal categories as per CRF]

EXAMPLE TABLE E (Enrollment)

Table 14.1.1.2
Enrolment by centre
xxx analysis set

Variable	Category /Statistic	Ethicon trt (n=99)	Comparator trt (n=99)	Total (n=99)
Centre	Wynnewood PA	9 (9.9%)	9 (9.9%)	9 (9.9%)
	Baltimore MD	9 (99.9%)	9 (99.9%)	9 (99.9%)
	Syracuse NY	9 (9.9%)	9 (9.9%)	9 (9.9%)
	Des Moines IA	9 (9.9%)	9 (9.9%)	9 (9.9%)
	Miami FL	9 (99.9%)	9 (99.9%)	9 (99.9%)
	Allentown PA	9 (99.9%)	9 (99.9%)	9 (99.9%)
	Augusta GA	9 (9.9%)	9 (9.9%)	9 (9.9%)
	Houston-1 TX	9 (9.9%)	9 (9.9%)	9 (9.9%)
	Jacksonville-1	9 (9.9%)	9 (9.9%)	9 (9.9%)
	Houston-2 TX	9 (99.9%)	9 (99.9%)	9 (99.9%)
	Camden NJ	9 (9.9%)	9 (9.9%)	9 (9.9%)
	Jacksonville-2	9 (99.9%)	9 (99.9%)	9 (99.9%)

[Centres shown for example only- will be town and either country or state code]

EXAMPLE TABLE G1 (General table 1, with total)

Table 14.x.x.x
xxxxxxxxxxxxxx
xxxxxx analysis set

Variable	Category /Statistic	Ethicon trt (n=99)	Comparator trt (n=99)	Total
Example for continuous data	Mean (std)	99.9 (99.9)	99.9 (99.9)	99.9 (99.9)
	Median (range)	99.9 (99.9, 99.9)	99.9 (99.9, 99.9)	99.9 (99.9, 99.9)
	Number (missing)	99 (9)	99 (9)	99 (9)
	95% CI of mean .	99.9 , 99.9	99.9 , 99.9	99.9 , 99.9
Example for discrete data	No data	9 (na)	9 (na)	99 (99.9%)
	Category 1 (as CRF)	9 (99.9%)	9 (99.9%)	99 (99.9%)
	Category 2 (as CRF)	99 (99.9%)	99 (99.9%)	99 (99.9%)
	Category n (as CRF)	9 (9.9%)	9 (9.9%)	99 (99.9%)

[This table is generally for baseline (pre procedure) data]

EXAMPLE TABLE G2 (General table 2, without total)

Table 14.x.x.x
xxxxxxxxxxxxxx
xxxxxx analysis set

Variable	Category /Statistic	Ethicon trt (n=99)	Comparator trt (n=99)
Example for continuous data	Mean (std)	99.9 (99.9)	99.9 (99.9)
	Median (range)	99.9 (99.9, 99.9)	99.9 (99.9, 99.9)
	Number (missing)	99 (9)	99 (9)
	95% CI of mean .	99.9 , 99.9	99.9 , 99.9
Example for discrete data	No data	9 (na)	9 (na)
	Category 1 (as CRF)	9 (99.9%)	9 (99.9%)
	Category 2 (as CRF)	99 (99.9%)	99 (99.9%)
	Category n (as CRF)	9 (9.9%)	9 (9.9%)

[This table is generally for primary and secondary endpoints that DO NOT need statistical testing]

EXAMPLE TABLE G3 (General table 3, with stats comparison)

Table 14.x.x.x
xxxxxxxxxxxxxx
xxxxxx analysis set

Variable	Category /Statistic	Ethicon trt (n=99)	Comparator trt (n=99)	Statistical summary			
				statistic	estimate	95% CI	probability
Example for continuous data	Mean (std)	99.9 (99.9)	99.9 (99.9)	Stat:Trt 1	99.99	(99.99,999.9)	
	Median (range)	99.9 (99.9, 99.9)	99.9 (99.9, 99.9)	Stat:Trt 2	99.99	(99.99,999.9)	
	Number (missing)	99 (9)	99 (9)	Stat:Diff	99.99	(99.99,999.9)	0.999
	95% CI of mean .	99.9 , 99.9	99.9 , 99.9				
Example for discrete data	No data	9 (na)	9 (na)	Stat	9.99	(9.99, 9.99)	0.999
	Category 1 (as CRF)	9 (99.9%)	9 (99.9%)				
	Category 2 (as CRF)	99 (99.9%)	99 (99.9%)				
	Category n (as CRF)	9 (9.9%)	9 (9.9%)				

[This table is generally for primary and secondary endpoints that need statistical testing]
[Stat refers to the statistical test defined in the SAP]
[Probabilities/stats test will only be carried out for tests defined in SAP]
[For continuous data items such as change from baseline will be included if defined in SAP. If that is to be tested it is usual to give visit summaries (no stats summary) and change from baseline (with stats summary)]
[Statistical analyses that produced the statistical summary will be included in section 16.1.9.2]

EXAMPLE TABLE HX (Physical exam / medical / surgical history)

Table 14.1.2.3
Physical exam / medical / surgical history
Safety analysis set

Variable	Category /Statistic	Ethicon trt (n=99)	Comparator trt (n=99)	Total (n=99)
Gastrointestinal	No data	9 (na)	9 (na)	9 (na)
	Normal	9 (99.9%)	9 (99.9%)	99 (99.9%)
	Abnormal	99 (99.9%)	99 (99.9%)	99 (99.9%)
Urogenital	No data	9 (na)	9 (na)	9 (na)
	Normal	9 (99.9%)	9 (99.9%)	99 (99.9%)
	Abnormal	99 (99.9%)	99 (99.9%)	99 (99.9%)
	Not done	9 (9.9%)	9 (9.9%)	9 (9.9%)
Skin	No data	9 (na)	9 (na)	9 (na)
	Normal	99 (99.9%)	99 (99.9%)	99 (99.9%)
	Abnormal	9 (99.9%)	99 (99.9%)	99 (99.9%)
	Not done	9 (9.9%)	9 (9.9%)	9 (9.9%)
Respiratory	No data	9 (na)	9 (na)	9 (na)
	Normal	99 (99.9%)	99 (99.9%)	99 (99.9%)
	Abnormal	99 (99.9%)	99 (99.9%)	99 (99.9%)
Cardiovascular	No data	9 (na)	9 (na)	9 (na)
	Normal	9 (99.9%)	9 (99.9%)	99 (99.9%)
	Abnormal	99 (99.9%)	99 (99.9%)	99 (99.9%)
Musculoskeletal	No data	9 (na)	9 (na)	9 (na)
	Normal	99 (99.9%)	9 (99.9%)	99 (99.9%)
	Abnormal	99 (99.9%)	99 (99.9%)	99 (99.9%)
	Not done	9 (9.9%)	9 (9.9%)	9 (9.9%)
Hepatic	No data	9 (na)	9 (na)	9 (na)
	Normal	99 (99.9%)	99 (99.9%)	99 (99.9%)
	Abnormal	9 (99.9%)	9 (99.9%)	99 (99.9%)

[Example layout. Actual categories will be as SAP, Table likely to be over 2 or 3 pages]

EXAMPLE TABLE L (Laboratory results)

Table 14.3.2.1
Laboratory results (<Parameters>, SI units)
Safety analysis set

Variable	Category /Statistic		Ethicon trt (n=99)		Comparator trt (n=99)	
Screening: WBC (x10^9/L)	Mean (std)		9.9	(9.9)	9.9	(9.9)
	Median (range)		9.9	(9.9-99.9)	9.9	(9.9-99.9)
	Number (missing)		99	(9)	99	(9)
	95% CI of mean	.	9.9	,9.9	9.9	,9.9
Post-op : WBC (x10^9/L)	Mean (std)		9.9	(9.9)	9.9	(9.9)
	Median (range)		9.9	(9.9-99.9)	9.9	(9.9-99.9)
	Number (missing)		99	(9)	99	(9)
	95% CI of mean	.	9.9	,99.9	9.9	,99.9
Difference:WBC (x10^9/L)	Mean (std)		9.9	(9.9)	9.9	(9.9)
	Median (range)		9.9	(-9.9-9.9)	9.9	(-9.9-99.9)
	Number (missing)		99	(9)	99	(9)
	95% CI of mean	.	-9.9	,9.9	9.9	,9.9
Screening: RBC (x10^12/L)	Mean (std)		9.9	(9.9)	9.9	(9.9)
	Median (range)		9.9	(9.9-9.9)	9.9	(9.9-9.9)
	Number (missing)		99	(9)	99	(9)
	95% CI of mean	.	9.9	,9.9	9.9	,9.9
Post-op : RBC (x10^12/L)	Mean (std)		9.9	(9.9)	9.9	(9.9)
	Median (range)		9.9	(9.9-9.9)	9.9	(9.9-9.9)
	Number (missing)		99	(9)	99	(9)
	95% CI of mean	.	9.9	,9.9	9.9	,9.9
Difference:RBC (x10^12/L)	Mean (std)		-9.9	(9.9)	-9.9	(9.9)
	Median (range)		-9.9	(-9.9-9.9)	-9.9	(-9.9-9.9)
	Number (missing)		99	(9)	99	(9)
	95% CI of mean	.	-9.9	,-9.9	-9.9	,-9.9

[Lab parameters will be as Protocol]
[SI units should be defined in SAP]
[Lab values with discrete data will just be summarised by visit, unless otherwise specified in the SAP]

EXAMPLE TABLE PD (Protocol deviations)

Table 14.1.1.3
Summary of protocol deviations
Safety analysis set

Variable	Category /Statistic	Ethicon trt (n=99)	Comparator trt (n=99)	Total (n=99)
Individual PD (^)	Yes	99 (na)	99 (na)	99 (na)
Any PD ($)	Yes	99 (99.9%)	99 (99.9%)	99 (99.9%)
Randomisation($)	Yes	9 (9.9%)	9 (9.9%)	9 (9.9%)
Study procedure($)	Yes	99 (99.9%)	99 (99.9%)	99 (99.9%)
Other ($)	Yes	9 (99.9%)	9 (99.9%)	9 (99.9%)
Major ($)	Yes	9 (99.9%)	9 (99.9%)	9 (99.9%)

[Categories will be as CRF]

^: total number of PDs
$: Number of patients with at least 1 PV in this category

EXAMPLE TABLE ST (Analysis sets)

Table 14.x.x.x
Analysis sets
xxx analysis set

Variable	Category /Statistic	Ethicon trt (n=99)	Comparator trt (n=99)	Total (n=99)
Safety	Yes	99 (99.9%)	99 (99.9%)	99 (99.9%)
ITT	Yes	99 (99.9%)	99 (99.9%)	99 (99.9%)
Per protocol	Yes	99 (99.9%)	99 (99.9%)	99 (99.9%)
	No- Major PV	99 (99.9%)	99 (99.9%)	99 (99.9%)

[Analysis sets as defined in SAP]