

## Data Management and CDISC Formatting for Transdermal Patches

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### ABSTRACT

Transdermal patch use is an alternative delivery method for medication that has many advantages to the user. One advantage of transdermal medication delivery is that it bypasses the gastrointestinal (GI) tract and goes directly to the location where it is needed; patches therefore tend to have fewer GI side effects than oral medication. Clinical trials to evaluate the safety and efficacy of transdermal products are a specialty area of investigation included in the Food and Drug Administration's Guidance's for Devices.

The Food and Drug Administration (FDA) regulations and guidance's mention study designs, objectives and measurement scales to evaluate the various aspects of transdermal patch performance. Some are the Fitzpatrick Skin Type, Patch Application Site Evaluation, Study Drug Administration, Adhesion, Discomfort, Pain, Irritation, and Adhesive Residue. This paper identifies and evaluates the inter-relatedness of each of these scale and data points as they apply to data management and statistical tasks of the electronic Case Report Form (eCRF), eCRF Completion Guidelines, Edit Checks, Randomization, and the Clinical Data Interchange Standards Consortium (CDISC) datasets.

Readers of this paper will get a broad understanding of the evaluation of transdermal patch use and a look at the interrelatedness of relevant forms and scales, as well as data management and statistical programming tasks for a clinical trial.

### INTRODUCTION

Each clinical trial for a transdermal patch will have a different focus based on its study objective(s) and some of the below information may need to be changed to suit the objective. Regardless of whether the study design is crossover or parallel, or the study objective is bioavailability, bioequivalence, dose ranges, dose proportionality, patch application sites, adhesion characteristics, heat exposure, water exposure, cumulative irritation and sensitization, or efficacy for a therapeutic population, an evaluation of the safety of patch use is consistently an essential part of these studies. Since study subjects are not taking drug during a Label Comprehension study it will not be reviewed here. Pharmacokinetic (PK) and pharmacodynamics (PD) blood draw forms are also not here but would follow the PK or PD planned time points needed for bioequivalence, bioavailability and dose range studies. Efficacy for a therapeutic population would be similar to what is here and geared towards that objective.

Data management along with the clinical team input provides the foundation tasks for a clinical trial. Their responsibilities include incorporating the dermal measurement scales into the eCRF to provide dermal safety data. The associated eCRF Completion Guidelines are instructions for a user entering data into the data collection software screens. In the broadest sense edit checks of the data are checks for accuracy with automatic checks, programmed checks, and manual checks. The Statistics department provides the randomization schedule for patch use which is often a multilevel process that will be discussed. Programming provides the final data in CDISC Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets needed for submission to the FDA or an international agency for consideration.

### DATA MANAGEMENT

#### ELECTRONIC CASE REPORT FORMS

The advantage of electronic data capture (EDC) is the shortened real-time data discrepancy management compared to that for paper data to be double data entered and reviewed. To evaluate the experience of transdermal patch use and its safety the eCRFs needed are for Study Drug Administration, Adhesion and Adhesive Residue. Depending on the study objective or the impact of a compound for patch use then the

evaluation of Discomfort, Pain, and Irritation can be captured as needed. Check for an existing FDA Guidance for a particular patch compound to determine their recommendations.

There are several considerations when designing dermal forms and the book of visit forms. Ordering dermal assessments as they are scheduled to be conducted facilitates efficient data capture and minimizes duplication of identifier information such as actual treatment date, time, and location information. Patch use considerations include: whether one or more than one patch is worn at a time, whether patch placement and / or replacement is allowed on one or various body locations, use of reinforcing tape, and moving a subsequent patch to a treatment naïve location. If a patch falls off or is removed within, say less than half the wear time then is a replacement patch allowed? Is reinforcing surgical tape allowed? If surgical tape is applied to a patch to keep it in place then would that applied tape get the same documented evaluations as a patch? For a long term study, if there is irritation at the original patch application site can the next patch application get applied to one or two treatment naïve sites? Do discomfort, irritation and pain get reported in those specific forms or as Adverse Events?

The schedule of patch use assessment forms are listed on Table 1. There are a few ways to organize eCRFs forms. One way is to group assessments based on the sequential timeframe of scheduled visit days; this allows an actual treatment and date of assessment to be entered once and allows for entry of the necessary individual actual time points. This streamlines treatment and visit date to be entered once for a set of assessments. Another way is to have separate forms for each assessment with the pre-printed scheduled visit days and times. This requires input of the actual treatment, visit dates and times on each form for each visit.

Sequential timeframe	Assessments / documentation								
	Fitzpatrick Skin Type	Patch Application Site Evaluation	Irritation	Treatment / Location	Adhesion	Discomfort	Pain	Activity at Time of Early Removal / Detachment	Adhesive Residue
Screening	x	x							
Prior to patch application			x						
Patch application				x					
During patch wear					x	x	x		
Post patch application time points			x		x	x	x		
Early or scheduled patch removal			x		x			x	
Post patch removal			x			x	x		x

**Table 1. The schedule of patch use assessment forms.**

### Study Population Considerations

Inclusion and exclusion criteria for a study's patient population eligibility to participate in a clinical trial can be based on the Fitzpatrick Skin Type and an Evaluation of the Patch Application Site. If a subject's skin is deeply pigmented patch application may cause changes in skin color and this is an issue to be avoided. If the patch application site is not suitable for a patch application this needs to be pre-determined. If one or more of these exist, is an acceptable protocol work around possible or not?

*Fitzpatrick Skin Type*

- I = Always burns easily, never tans
- II = Always burns easily, tans minimally
- III = Burns moderately, tans gradually
- IV = Burns minimally, always tans well
- V = Rarely burns, tans very well
- VI = Never burns, deeply pigmented

*Patch Application Site Evaluation*

Was patch application site evaluation performed? Yes No

If No, specify reason

Tattoos in patch application area? Yes No

Excessive Hair in patch application area? Yes No

Sunburn in patch application area? Yes No

Skin Evaluation of entire back: Normal Abnormal

If abnormal, indicate findings

Is the patch application area acceptable for patch application? Yes No

**Visit Information**

After a subject is initially randomized to a treatment group or treatment sequence, the planned and actual treatment information can be listed once per patch application and applied to the assessed dermal safety scales. There can be one form for each planned study day or a set of forms that allows for multiple study days of data to be captured. The associated planned time points for each dermal assessment may differ and will need to be listed with each dermal assessment as a form or as a log, depending on the design or software considerations. Within this structure each of the actual dates and time points can be listed as applies to each of the dermal assessments as they occur.

*Visit Information*

Randomized Study Treatment

Actual Treatment

Patch Application Site: Hip

Side: Left Right

Planned Study Day

Actual Assessment Date MM/DD/YYYY

Planned Time points

Actual Assessment Time (24 hour clock) HH:MM

**Irritation Assessment**

Irritation assessments are captured before and after patch use. Irritation assessments are the focus of the Repeat Insult Patch Test (RIPT) Study that evaluates the effect of wearing a patch at the same location over an extended period of time. For an RIPT study the duration of post patch removal assessments may continue for a few days and collecting photographic evidence is recommended.

*Irritation*

Planned time point (prior to patch application and post patch removal time intervals)

Was the assessment performed? Yes No

If No, specify reason

Assessment Date MM/DD/YYYY

Assessment Time (24 hour clock) HH:MM

Was Photograph Taken? Yes No Not Applicable

**Dermal Response Score**

- 0=No evidence of irritation
- 1=Minimal erythema, barely perceptible
- 2=Definite erythema, readily visible; or minimal edema or minimal papular response
- 3=Erythema and papules
- 4=Definite edema
- 5=Erythema, edema, and papules
- 6=Vesicular eruption
- 7=Strong reaction spreading beyond test (i.e., application) site

**Other Effects**

- N (0) = No other effects observed
- A (0) = Slightly glazed appearance
- B (1) = Marked glazed appearance
- C (2) = Glazing with peeling and cracking
- F (3) = Glazing with fissures
- G (3) = Film of dried serous exudates covering all or part of the patch site
- H (3) = Small petechial erosions and/or scabs

**Study Drug Administration**

Study Drug Administration occurs at planned time points for a specific treatment, on a specific date, time and body location. Sometimes a patch application is attempted unsuccessfully; this is important to note. If a study subject removes a patch before the scheduled date and time for patch removal, note the date, time and reason for early removal.

To facilitate smooth flowing data entry, list items on the CRF in the order that events occur. For example, for single dose studies it is clear that a patch gets applied first then its removed and that order works. For multi-dose studies after the first patch is applied, the first patch must be removed before the next patch is applied. For this situation reverse the order to have patch removal first then patch application to follow. In this case, for the first Study Drug Administration form where patch removal comes before patch application have a possible patch removal response to be Not Applicable. Also, for the last Study Drug Administration form in a series where patch application is present have a possible patch application response to be Not Applicable.

The need for details about a patch application failure will depend on a study's purpose. For a phase 1 or 2 study it might be important, for a phase 3 study most of the possible responses will be known and for the best case scenario resolved.

*Patch Application*

Scheduled Study Day

Planned time points

Assigned Study Treatment / Group / Sequence

Actual Treatment

Was the patch applied? Yes No

If No, was there a patch application failure? Yes No

If No, specify reason

If Yes, provide reason for patch application failure or patch was not applied:

Patch did not fully adhere to the skin upon application

Patch wrinkled during application

Patch could not be applied because it was removed from the pouch incorrectly

Patch could not be applied because there was adhesive transfer to the liner

Patch was damaged when removed from the pouch

Other, specify

Date of patch application MM/DD/YYYY

Time of patch application (24 hour clock) HH:MM

Route: Transdermal

Location: Hip

Side: Left Right

## Discomfort Assessments

Discomfort is evaluated at post-dose time points while the patch is adhered to the skin. Adults are evaluated for discomfort with the descriptor discomfort scores from 0 (no discomfort) to 4 (patch not present).

### *Discomfort Assessment*

Scheduled Study Day

Assessment date MM/DD/YYYY

Planned Assessment time points (patch wear intervals) (24 hour clock) HH:MM

Was the assessment performed? Yes No

If No, specify reason

Discomfort score

0=No discomfort

1=Mild discomfort

2=Moderate but tolerable discomfort

3=Severe, intolerable discomfort

4=Patch not present

Describe Discomfort

## Pain Assessment

A pain assessment is captured differently for children than for adolescents and adults. Teenagers and Adults assess pain based on the Visual Analog Numeric Pain Scale Score that progresses with increments of one from 0 (no pain) to 5 (moderate pain) to 10 (worst possible pain). Children aged 6-12 years of age provide a pain assessment that is also measured from 0 to 10, they choose from among the six Wong-Baker Faces; the Scale progresses in increments of two starting with a score 0=a happy face for 'no hurt', 2='hurts a little bit', 4='hurts a little more', 6='hurts even more', 8='hurts a whole lot' and a score 10=a crying face for 'hurts worst'. The child would choose the face that best describes their level of pain.

## Adhesion Assessment

An assessment of patch adhesion for the duration of the recommended patch wear time is critical to effective drug delivery. The submission of photographic documentation is recommended for studies where adhesion is a primary objective.

Trained staff evaluate the percentage of patch adhesion as measured by a 5-point scale from 0 (=>90% adhered) to 4 (patch detached). If study subjects are scheduled to be home for a full day or more while wearing a study patch, study subjects are instructed to check the patch for skin adherence throughout the day and report to study staff immediately if a patch detaches partially or completely. Capturing the activity at the time of partial or complete detachment helps paint a picture of the situation where it occurred, and may highlight unforeseen circumstances.

### *Adhesion Assessment*

Scheduled Study Day

Assessment date

Planned time points (prior to patch removal)

Actual Assessment time (24 hour clock) HH:MM

Was a photograph taken? Yes No

Was assessment performed? Yes No

If No, specify reason

Adhesion Score (when score = 4, ensure date/time of detachment is recorded):

0= > 90% adhered (essentially no lift off the skin)

1= > 75% to < 90% adhered (some edges only lifting off the skin)

2= > 50% to < 75% adhered (less than half of the system lifting off the skin)

3= > 0% to < 50% adhered but not detached (more than half the system lifting off of the skin without falling off)

4= 0% adhered-patch detached (patch completely off the skin)

Activity/Reason for partial detachment (provide only If Adhesion Score is > 1)

Did the patch fully detach? Yes No

If yes, provide the following information:

Date the patch fully detached

Activity at time of detachment

Time the patch detached (24 hour clock) HH:MM

Time the patch detached is unknown:

Was replacement patch applied? Yes No

If No, specify reason

If Yes, Date of patch replacement

Time of patch replacement (24 hour clock) HH:MM

Location of patch application

## Patch Removal

If the patch is removed as scheduled, indicate the actual date and time of patch removal. If a study patch is removed before the scheduled date and time for patch removal, note the date, time and reason for early removal. If the reason for removal is because of Irritation or Discomfort, then either the indicated form needs to be completed or it gets reported as an Adverse Event.

### *Patch Removal*

Date patch removed MM/DD/YYYY

Time Patch removed (24 hour clock) HH:MM

Is patch removal time unknown? Yes

Was patch from previous visit removed as scheduled? Yes No Not Applicable

If No, was this an early removal? Yes No

If yes, specify the reason?

Irritation

Discomfort

Other, specify

## Adhesive Residue

Trained site personnel evaluate adhesive residue using either the 4-point scale or the 5-point scale to assess the percentage of an adhesive residue or treatment material that remains on the skin after a patch is removed. This assessment may be repeated after the required post patch removal irritation assessment and the application site is cleaned.

### *Adhesive residue score*

Scheduled Study Day

Assessment date MM/DD/YYYY

Planned Assessment time points (immediately post patch removal) (24 hour clock) HH:MM

Was the assessment performed? Yes No

If No, specify reason

Actual assessment time (24 hour clock) HH:MM

Adhesive Residue Score (4-point scale percentages)

0=None (0%)

1=Light (<25% of patch site)

2=Medium (=>25% to => 75%)

3=Heavy (=>75% of patch site)

Not Done

Adhesive Residue Score (5-point scale percentages)

0=None (0%)

1=Minimal (<10% of patch site)

2=Light ( $\geq 10\%$   $\leq 25\%$  of patch site)

3=Medium (>25% to  $\leq 50\%$  of patch site)

4=Heavy (>50% of patch site)

## Investigator's Interpretation of Sensitization

An objective of an RIPT study includes an investigator's assessment of sensitization at the patch application site.

### *Sensitization*

Did the Subject exhibit a suspected sensitization reaction to any of the test articles? Positive Negative Equivocal

## Heating Pad Application and Removal

Heat studies evaluate the effect of heat in the form of a heating pad on the study drug's delivery to the study subject. It is important to evaluate that the temperature of the heating pad as the protocol defines it is maintained for the study duration and that the heating pad stays in place for the protocol defined evaluation time.

### *Heating Pad*

Was heating pad applied? Yes No

If no, reason not applied

Date of Heating Pad Application MM/DD/YYYY

Time of Heating Pad Application (24 hour clock) HH:MM

Planned Assessment time points (patch wear intervals) (24 hour clock) HH:MM

Was the assessment performed? Yes No

If No, specify reason

Temperature of Heat Source (Fixed Unit) C

Time Heating Pad Removed (24 hour clock) HH:MM

Was the heating pad removed prior to the scheduled n-hour removal time? Yes No

If Yes, specify reason

## Water Exposure

For a study evaluating the effect of water exposure, capture a picture of the patch before and after water exposure to see the effect of the water on the patch. Do this before and after the patch adhesion assessment. After water exposure, be sure to capture the date, time and activity when a patch partially (5-point adhesion score = 2 or 3) or completely (score = 4) detached from the skin. Also, for an early patch detachment capture if the patch was recovered or lost.

### *Water Exposure*

Did the subject participate in a water exposure activity? Yes No

Water Activity: Swimming Showering Bathing Other specify

Start Time (24 hour clock) HH:MM

End Time (24 hour clock) HH:MM

Additional Comments

## ECRF COMPLETION GUIDELINES

The case report form completion guidelines bridge the gap between the study protocol and the data collection process; it explains the activities for CRF completion such as forms to complete, data entry field formats, correction methods, and form sign off. Each data entry form's screen is imaged as a visual with instructions for each data entry field on each page in the CRF booklet with detailed instructions on CRF completion for all practical scenarios. This helps to ensure completion of all required data fields and explains 'if this then that' contingencies for data completion.

## EDIT CHECKS

The CDISC Glossary v1.1 defines edit checks as "An auditable process, usually automated, of assessing the content of a data field against its expected logical, format, range, or other properties that is intended to reduce error."

Edit checks include automatic checks, programmed checks and manual checks to identify illogical, incomplete or inconsistent data. With electronic data entry there are automatic data checks that appear immediately at the time of data entry of one variable. Programmed checks can compare two or more variable entries within a form, across forms or to see that another form is completed, if it is indicated based on the circumstances. Manual checks can be from generated data reports for a project manager or a site monitor for risk based monitoring.

### Automatic Checks

The usual automatic checks are for individual variables to evaluate entry of a valid date, time or format for a categorical variable.

### Programmed Checks

Programmed checks are conditional checks that check across two or more variables within a form or across forms. The more complicated the patch study the more important the programmed checks become to obtaining quality data.

All dermal form's actual dates need range checks; are they within the study period, that is, greater than or equal to the screening date, less than or equal to the last date of study contact and in a logical sequence that increases as planned? Times are entered based on the military clock and need to be in a logical sequence that increases as planned.

If on the same form, a text variable response is conditionally required, that would have a programmed check for its completion. For example, Yes or No and Specify questions need to see that the specify field is entered as needed and completion of other relevant conditional text fields are checked this way. Programmed checks that cross forms are sometimes delayed in appearing which can be confusing at first



try; this is because the second or third form and / or data field needs to be completed before an error message gets activated. In this case, multiple reviews of the data for completion and logical responses may be needed.

The easiest patch study data to review is for a one patch application study. The completion of dermal forms is clearly for that one patch. Data checks for multiple patches and patch locations and changing locations over time on multiple dermal assessments can get very complicated very quickly.

If a patch application alternates from one side of the body to the next over time and subsequent applications, the sequence of events predictably alternate from say, left to right. This can be pre-printed on forms as planned and if the actual is different that can be indicted.

If more than one patch is applied simultaneously, then dermal assessments need to clearly indicate which patch is being assessed by clearly identifying each patch as, for example patch site 1, 2, 3 or word text as top, middle, bottom for a particular body location. When this kind of study continues over an extended period of time, it is mission critical that patch identifiers are clearly indicated on their associated dermal forms. This can be accomplished by dynamically populating patch identifiers on the relevant related dermal forms to be completed. Be sure the dynamically populated variables are being populated correctly else this could create havoc in the data.

If mid-way through a planned patch application time one of one, two or three patches detaches or is removed early and a replacement is allowed then both patches need to be clearly identified and assessed. The detached patch needs to be clearly identified as the original patch and the replacement patch on dermal assessments.

If the protocol has multiple patch sites, and the patch site varies for each subsequent patch applied from one patch application date and time to the next, the documentation must clearly identify each patch as study personnel write their replies or have the patch identifiers carried over to the dermal forms to be completed.

### **Manual Checks with or without Generated Reports**

To ensure subject protection and study quality for items too complicated or out of scope to be reviewed by an automatic check or a programmed check, manual checks by a data monitor can be conducted with or without generated reports.

There are two approaches to data review; either one or the other or a combination of the two methods can be implemented and must be clearly described in the study's Data Monitoring Plan. The traditional method is 100% data verification by a data monitor(s) who visit a study site(s) to review source data and ensure that data entered or missing on eCRFs match the source data. The other approach is centralized monitoring based on focused reports generated by a study's sponsor, data manager or statistician. A data monitor can improve his or her effectiveness on-site by prioritizing monitoring visits with pre-defined reports about critical study parameters and processes necessary to achieve study objectives. The FDA has recommendations on how to develop and implement this type of study-specific monitoring plan and says that centralized monitoring activities can identify more than 90% of the findings identified during on-site monitoring visits. (Risk Based Monitoring, August 2013, p 8 of 22)

### **Topics for Generated Reports**

If data privacy and security concerns as well as technological challenges are overcome and a sponsor has access to a subject's electronic records, data checking would be an electronic comparison of study data with the electronic records. Else on-site data monitors can focus their data review efforts on the report findings for critical data points that must be accurate to evaluate the trial's objectives. There might be variables with missing data, inconsistent data, data outliers, and potential protocol deviations. They can list text fields to be reviewed for a logical reply to text fields. Study performance metrics can check data about study drug administered, dispensed and returned the assigned product. For a multi-site study statistical analyses can identify unusual data distributions within and between study sites, such as too little variance. FDA inspection and review experiences find that infrequent errors in non-critical data are unlikely to alter the FDA's conclusions about whether a product is safe and effective and whether participants' safety was appropriately monitored. (Risk Based Monitoring, August 2013, p15 of 22)

The type of monitoring (e.g., on-site, centralized), and extent e.g., comprehensive (100% data verification) versus targeted or random review of certain data (less than 100% data verification) of monitoring activities will depend to some degree on a range of factors, considered during the risk assessment, including the following: Complex studies will require extensive review e.g., adaptive designs, stratified designs, or multiple patch studies.

Objective endpoints are suitable for remote verification. For subjective endpoints, subjects who did not follow the protocol, seriously ill or vulnerable populations or geographically different medical practices consider an on-site review of source data.

## STATISTICS

Randomization of subjects and patch location is a multilevel process with consideration for the subjects to be randomized to a treatment, to the anatomical patch location or locations and to the side of the body that may or may not alternate. See the author's explanation of this process in the referenced paper at the end of this manuscript.

## STATISTICAL PROGRAMMING

There are several CDISC's SDTM domains for Medical Devices (SDTMIG-MD) and an associated Implementation Guide v1.0. Subsequent Implementation Guide updates became available after this publication. Since a patch is technically a drug delivery system that is included here as a medical device on the subject, these could potentially be useful. They appear to be more for a device that enters the body that also delivers a drug.

DEVICE IDENTIFIERS (DI)  
DEVICE IN-USE (DU)  
DEVICE EXPOSURE (DX)  
DEVICE EVENTS (DE)  
DEVICE TRACKING AND DISPOSITION (DT)  
DEVICE-SUBJECT RELATIONSHIPS (DR)  
DEVICE PROPERTIES (DO)

In general for clinical trials with transdermal patch(s) choose one of the following two domains from the subsequent SDTMIG version 3.2.

FINDINGS ABOUT (FA)  
SKIN RESPONSE (SR)

Review each domain to see which one or more are relevant for your data. The Study Drug Administration data would be captured in Drug Exposure (EX) domain. All the dermal safety assessment data can be captured in one of these domains for ease of reference, either Findings About (FA) or Skin Response (SR). Adverse Events would be captured in the Adverse Event (AE) domain.

The ADaM domain that captures the dermal data would correspond to the SDTM version and be either ADFA or ADSR.

If there is any question about which domain is relevant to capture the data, be in correspondence with the regulatory agency to ask which domain is preferred.

## CONCLUSION

Patch study designs and objectives determine the needed measurement scales to evaluate patch performance.

Data management along with the clinical team's input delivers the foundation tasks for efficient clinical trial data capture and data checks.

Patch use studies have the unique consideration for treatment randomization that also includes anatomical location that may be the same or change for longer duration studies.

There are a handful of CDISC domains to capture patch data, as the data requires.

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