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# Review of hot flash diaries

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# **Abstract**

Currently, there is only 1 published hot flash diary. This diary rates hot flash severity according to 4 categories: Mild, Moderate, Severe, and Very Severe. The descriptions of these 4 severity categories are located on a separate form from the main data form. For each 24-hour period, subjects record the number of hot flashes experienced for each of the 4 severity categories either by recollection or from a separate data source on which hot flashes have been tallied. This diary has been validated but does not conform to the FDA & EMEA Guidance for Industry. After we observed a high percentage of subjects reporting confusion when using this 4-category diary, we constructed and used a hot flash diary containing 3 severity categories that offered real-time recording of hot flashes, contained all severity definitions on the principle data form and also conformed to the FDA & EMEA Guidance for Industry. We compare these 2 diaries here and provide a sample of the 3-category diary, which has not been formally validated but is considered valid by the FDA & EMEA in support of drug approval. Either diary is acceptable for use in clinical trials.

## **Keywords**

hot flash; hot flush; diary; clinical trial; methodology; menopause

## Introduction

Hot flash clinical trials typically utilize a paper diary in order to assess subjects' hot flash frequency and severity. The most commonly used diary in academic-initiated hot flash clinical trials assesses 4-categories of hot flash severity (Mild, Moderate, Severe, and Very Severe), the definitions of which were compiled from subjects' perceptions.[1] For industry-

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initiated hot flash trials, the Food & Drug Administration (FDA) and the European Medicines Agency (EMEA) guidelines require hot flash severity to be assessed using 3-categories (Mild, Moderate, and Severe), the definitions of which were compiled from an FDA advisory committee.[2]

After we completed an initial hot flash clinical trial that used the 4-category diary[3], the Principal Investigator for this study noted that many subjects (approximately 50% from her recollection) reported confusion regarding the hot flash severity definitions included with this diary. This prompted us to develop and use a 3-category diary that conformed to FDA and EMEA guidelines. We report here on our development and use of this 3-category hot flash diary and compare its features directly with those of the 4-category diary.

# **Methods**

In development of the 3-category diary, the definitions for Mild, Moderate, and Severe hot flashes and night sweats were taken from the FDA Guidance for Industry[2] and the NIH hot flash workshop[4], respectively, and included on each diary (Figure 1). The EMEA guidelines[5] are identical to the FDA guidelines.

In order to support real-time subject recording of hot flashes, 48 empty circles were placed in each hot flash severity category for each calendar day. Each circle represented the occurrence of a distinct hot flash event when filled in by the subject. Subjects were instructed to keep the diary with their person at all times possible and to record each hot flash immediately after it occurred in order to reduce errors secondary to memory recall. Night sweats were to be recorded no later than that morning upon awakening to start a new day. If no hot flashes occurred for a full 24 hours, a separate circle would need to be filled in. It was explained to subjects that this was the only way for the research team to distinguish between the absence of hot flashes and a subject's failure to record hot flashes over a full day.

The diameter and spacing of the circles were chosen to interface with digital scanning software employing Optical Mark Recognition (OMR) to identify positively indicated hot flash episodes by the research participant.[6] In the circumstance where a subject mistakenly recorded a hot flash using an ink pen, the subject was instructed to place an X through the marked circle. During the data validation step of the scanned diaries, such events were easily detected and discounted from the record.

This 3-category diary was then used in 2 randomized controlled trials (RCTs) enrolling 151 subjects in total.[7-8] The 3-category diary (Figure 1) interfaced well with OMR scanning software. There was never an occasion when all 48 circles were filled in over a single day for any severity category among all of the diaries. Thus, there was no potential for hot flashes not being recorded due to lack of space on the diary. The Principal Investigator for these RCTs did not recall any subjects reporting confusion when using this 3-category diary.

The 4-category diary (Figure 2) and its hot flash severity definitions (Figure 3) are provided for direct comparison to the 3-category diary (Figure 1) and discussed.

## **Discussion**

The 3-category diary provided in Figure 1 is the first published hot flash diary that conforms to the FDA & EMEA guidelines. Besides this important feature, this diary also has several other unique qualities (such as supporting the real-time recording of hot flashes, requiring subjects to confirm that a day is free of hot flashes, including the severity category definitions on the same form as where hot flashes are recorded, and being designed to

interface well with OMR scanning software) that should help with the accuracy of subjects' hot flash recording and the accuracy of the digitalized hot flash record. This diary has not been formally validated. Nevertheless, the 3-category diary is considered valid by the FDA & EMEA in support of drug approval.

In contrast, the 4-category diary does not conform to FDA & EMEA guidelines, does not support real-time hot flash recording, does not include hot flash severity definitions on the main data form, and does not interface with OMR scanning software. The 4-category diary has, however, been formally validated.[1]

Among the differences between these 2 diaries, the most significant one relates to the hot flash severity definitions. The FDA & EMEA guidelines have very simple definitions for the 3 hot flash severity categories (Figure 1). In stark contrast, the severity definitions included with the 4-category diary (Figure 3) are highly detailed, lengthy, and contain much overlap. For example: embarrassment, change in heart rate, removal of clothing, and opening of windows are all listed under both Moderate and Severe hot flash definitions for the 4-category diary.

# Conclusion

The 4-category hot flash diary has the advantage of being formally validated while the 3-category diary's main advantage is with the simplicity of the severity definitions that comply with FDA & EMEA guidelines. Either hot flash diary is acceptable for use in clinical trials.

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SUBID	<b>DAILY</b> Fill in the approp at all times. Night	riate circle imme	diately after you i	have a hot flash.	Keep this sheet w	vith you O Stud	Study Period ly Period 1 ly Period 2
DATE (dd/mm)	/	/			/	/	
DAY	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
MILD: Sensation of heat without sweating/dampness.  If at night, you don't wake up, but later notice damp sheets or clothing.							
MODERATE: Sensation of heat with sweating/dampness, but able to continue current activity. May briefly fan yourself. If at night, you wake up because you are hot and/or sweating, but no action is necessary other than rearranging the bed sheets.	000000	000000	000000	000000	000000	000000	
SEVERE: Sensation of intense heat with sweating causing disruption of current activity. If at night, you wake up hot and sweating and need to take action (e.g., removing layer of clothes, open the window, or get out of bed).						000000	000000
If there were NO HOT FLASHES all day and night, fill in this circle.	0	0	0	0	0	0	0
STUDY WEEK: Page 1 of 1							

**Figure 1.**3-Category Hot Flash Diary

DAILY PATIENT QUESTIONNAIRE: DOUBLE-BLIND PHASE											
No tablets this week											
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7**				
Number of today's hot flashes that were mild, moderate, severe, or very severe? Total number	mild moderate severe very severe	_ mild _ moderate _ severe _ very severe	mild moderate severe very severe	_ mild _ moderate _ severe _ very severe	mild moderate severe very severe	mild moderate severe very severe	mild moderate severe very severe				
of hot flashes today*											
Date week stoppe  Do you have any  appetite los	of the following	symptoms?:		abnorm	al sweating	no	yes				
sleepiness				constip		no	yes				
dizziness	nausea no yes dizziness no yes			nervous	• •	no	yes yes				
	atigue) no no no	ye	s	mood c			yes				
Comments:											
Blood Pressure _		1	Date blood press	sure obtained:	/	-/	_				

**Figure 2.**4-Category Hot Flash Diary

#### PATIENT INFORMATION SHEET

### HOT FLASH DEFINITIONS FOR THE FEMALE PATIENT

Please refer to these examples of hot flashes that have been given by cancer survivors in previous studies when describing their hot flash severity. One or more of these descriptions may help to categorize your hot flash as mild, moderate, severe, or very severe.

Duration: Lasting less than 5 minutes Physical symptoms: Warmth, felt uncomfortable, red face Emotional symptoms: Not expected Action needed: Usually no action taken

#### MODERATE

Duration: Lasting up to 15 minutes

Duration: Lasting up to 15 minutes
Physical symptoms: Head, neck, ears, or whole body felt warm; tense, tight muscles; clammy (wet skin; a change in heart rate or rhythm (heart speeds up or changes beat); some sweating; dry mouth Emotional symptoms: Felt irritated, felt agitated (restless), felt as though energy was drained out, felt embarrassed when having a hot flash in front of others, felt tired, felt annoyed
Action needed: Needed to use a fan, awakened sometimes at night, needed to uncover, took off layers of clothing, drank water, opened the windows even when cold outside, wore lighter clothing

Duration: Lasting up to 20 minutes
Physical symptoms: Warmth, sometimes described as a raging furnace or burning up; a change in heart
rate or rhythm (heart speeds up or changes beat); felt faint; headache; severe sweating; weakness, a
pricking, stinging sensation over skin; chest heaviness
Emotional symptoms: Embarrassment, anxiety, feelings of having a panic attack
Action needed: Needed to stop what was being done at that time, usually awakened at night and
removed covers, needed to remove clothes, opened windows, kept the house a cooler temperature,
frequently used fans

#### VERY SEVERE

Duration: Lasting up to 45 minutes
Physical symptoms: Boiling heat, rolling sweat, difficulty breathing, felt faint, felt dizzy, feel and/or legs cramping, a change in the heart rate or rhythm (heart speeds up or changes beat), felt slightly sick

Emotional symptoms: Felt distressed, had the urge to escape, had difficulty functioning
Action needed: Awakened frequently at night, needed to change sheets and pajamas, needed to take a cold shower, needed to hold ice on skin

Figure 3. Severity Definitions for 4-Category Hot Flash Diary