

Adherence Assessment Using Medication Weight in a Phase IIb Clinical Trial of Difluoromethylornithine for the Chemoprevention of Skin Cancer

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Abstract

Objective: Adherence is a common and essential measurement in clinical trials. This study evaluates the association between participant self-reported study diary records and the weight of the medication vessel at each study visit, in the setting of a phase IIb topical chemoprevention trial.

Methods: One hundred and twenty-four eligible participants were randomized to one of four arms [34 to difluoromethylornithine (DFMO) plus triamcinolone, 31 to DFMO plus placebo, 31 to placebo plus triamcinolone, and 28 to double placebo] for 6 months of treatment for actinic keratosis. Adherence was assessed at each clinic visit by weighing each tube of dispensed and returned medication and the participant's study diary.

Results: Self-reported adherence was consistently higher than adherence measured by returned medication weight

(96.5% versus 71.3%, 94.6% versus 82.4%, 95.3% versus 69.5%, and 95.8% versus 66.8% for DFMO, DFMO placebo, triamcinolone, and triamcinolone placebo, respectively; $P < 0.001$). Most participants (59.2%) recorded 100% adherence on the study diary; however, using the weight adherence, only 10.2% were completely adherent to the study regimen.

Conclusions: Self-reported diary measures seem to overestimate adherence when compared with weighing the returned medication vessel. It is recommended that future clinical trials involving topical applications incorporate medication weights as a primary measure of adherence because it is objective, quantitative, inexpensive, noninvasive, and easy to use. (Cancer Epidemiol Biomarkers Prev 2005;14(11):2579–83)

Introduction

The internal validity of results from cancer prevention clinical trials is highly dependent on adequate adherence to the study intervention agent(s). Previous work in the field of adherence to clinical trial regimens has included, but is not limited to, the usefulness of various adherence measures and the use of biological markers or tracers (1, 2). Chemoprevention clinical trials have used a variety of these measures to evaluate participant adherence to the study regimen. These have included capsule count, self-report, electronic monitors, biological markers, diaries, and questionnaires (3–6). Each of these methods has their respective strengths and weaknesses. Study diaries are inexpensive and convenient for both studies of topical or oral agents; however, measurement of adherence using the study diary is subject to reporting errors and bias, and adherence is consistently overestimated. Participants who do not adhere to the study regimen do not tend to self-report nonadherence (3). Biological markers may be more accurate, but are costly and require additional tissue or blood samples and further laboratory testing. Capsule count is the most common measure of adherence used in cancer prevention and control research studies using oral tablet or capsule medications (3, 4), but it is not possible to implement "counting" in studies of topical agents, such as skin cancer prevention trials, in which the daily dose is not premeasured. One alternative to capsule count in studies of topical agents is to evaluate medication intake by evaluating the study medication used by

weighing the medication vessel (e.g., tube) at the time it is dispensed and at the time of return. These various measures of adherence do not each lie on the same underlying scales (e.g., daily use versus daily amount of agent use), which may lead to misinterpretation when reporting results simply under the general term "adherence" without clarifying the methods of measurement and of analysis. Unlike studies of oral capsule or tablet medications, adherence to topical agents is more likely to be subject to variability in the quantity of agent used each day; thus, daily use and the overall quantity of medication applied may not be equivalent between participants. It is essential that an accurate, inexpensive, and noninvasive method of evaluating adherence to clinical trial regimens be developed and described that can be applied in clinical research involving topical medications.

The purpose of this article is to evaluate a method of adherence assessment that uses the weight of dispensed and returned medication, and to compare these weight adherence assessments with values from study diary self-report measures, which are currently used for assessment of adherence to topical agents in phase IIb skin cancer chemoprevention studies at the Arizona Cancer Center.

Materials and Methods

Difluoromethylornithine Study. One hundred and thirty six (136) study participants were enrolled into a phase IIb study to evaluate the safety and efficacy of topical difluoromethylornithine (DFMO) with and without a topical corticosteroid cream (triamcinolone 0.1%) in the treatment of actinic keratoses on the forearms (DFMO Study) from September 2000 through July 2002. The study was approved by the University of Arizona Institutional Review Board. Informed consent was obtained from all participants.

DFMO was supplied by ILEX Oncology, Inc./Marion Merrill Dow (San Antonio, TX) and was weighed and mixed

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by blender into a 10% w/w concentration in hydrophilic ointment USP. The vehicle alone was used as the control. Triamcinolone (0.1%) was supplied in a cream base by Fougera, Melville, NY. Eucerin (a commercially available cream) was used as the control for triamcinolone. Each agent and placebo was transferred to polyethylene-lined, 30 g metal ointment tubes, which were then crimp-sealed and uniquely barcoded for identification.

The primary objectives of the DFMO Study were to determine if 10% DFMO could reverse moderate to heavy actinic keratosis as assessed by histopathology and clinical evaluation, and if DFMO could improve surrogate end point biomarkers of proliferation, progression, p53 expression, and apoptosis as assessed by automated image analysis. Triamcinolone was evaluated to determine if its application would reduce DFMO-induced skin irritation. The DFMO Study was funded by the National Cancer Institute as a part of the Skin Cancer Chemoprevention Program Project (CA27502).

Of the 136 enrolled, 124 were found to be eligible and were randomized in a double-blind fashion to one of four treatment groups (34 participants randomized to DFMO + triamcinolone, 31 to DFMO + placebo, 31 to placebo + triamcinolone, and 28 to double placebo). Eligible participants were healthy men and women >17 years of age with at least three clinically visible actinic keratosis lesions on each lower posterior forearm. Female subjects of childbearing potential agreed to practice an effective method of contraception during the entire study period. Patients with a history of invasive cancer within the past 5 years, and those with a history of skin cancer on the forearms at any time, were excluded from this study. Reasons for nonrandomization of the 12 participants enrolled to this trial included: five due to non-actinic keratosis diagnosis at enrollment, two moved out of the area, one had a reaction to the sunscreen during the run-in period and was not randomized, two had illnesses that were contraindicated per study protocol, one participant withdrew due to time limitations for study participation, and one was lost to follow-up.

Participants were instructed to apply study cream daily. One inch of DFMO (or placebo) was to be applied at dinnertime to each forearm. At least 1 hour after DFMO or placebo application, participants were instructed to apply 1 in. of triamcinolone (or placebo) to each forearm at least 1 hour before they went to bed. Application of 1-in. measurements of cream was demonstrated by clinic staff using a tube of placebo. One inch was measured across the participant's fingers and the clinic staff then dispensed and applied the 1-in. quantity of cream to their own arms. Clinic staff then observed the participant perform this procedure with the placebo. Following this initial training visit, participants did not put on the actual study cream until that night at home. Participants were also instructed to use sunscreen every morning regardless of expected sun exposure and at least 30 minutes prior to being outdoors.

Adherence Measurements. Participant adherence to topical study medication was assessed by weighing each tube prior to being dispensed and when returned at monthly clinic visits. Adherence was measured at any interim clinic visits (e.g., if a participant returned to the clinic at additional time points between the regularly scheduled monthly visits). Clinical research staff weighed the dispensed and returned tubes using an Ohaus CT-600S balance. Participants were given a new tube of study medications at each monthly clinic visit. Participants were instructed to return the used tubes at each visit and were instructed to record daily applications of the study medications. To determine the "gold standard" for the weight of study medication that should have been used by participants, a series of 1-in. weight measurements were made in the clinic by research staff. Five clinical research staff

members were instructed to squeeze a 1-in. amount of study cream onto each of six sheets weighing paper for each study agent. These 120 samples (30 for each study agent) were then weighed individually to determine the typical daily weight of each medication used in this study (DFMO, triamcinolone, and each control).

Statistical Methods. The gold standard was determined by taking the mean value of the clinical staff-measured 1-in. weights for each agent. The difference between dispensed and returned medication weight was calculated for each participant at each clinic visit for each agent to obtain the actual used medication weight. The gold standard 1-in. mean weight was multiplied by the number of days in the evaluation period for each participant and for each agent to obtain an expected medication weight if a participant was 100% adherent. To obtain the adherence percentage for medication weight, the actual medication weight of each agent used per arm was then divided by the expected medication weight for each subject and multiplied by 100.

The study diary provided the number of days the participant reported using each medication during each evaluation period. The number of days reported was divided by the number of days in the evaluation period and multiplied by 100 to obtain an adherence percentage for each agent used by each participant. In the case of a nonreturned medication tube or study calendar, the respective adherence value for that visit was noted as missing and not included in the analysis. The unit of analysis for adherence was the monthly visit of each study participant (participant visit).

The statistical package SPSS 12.0.1 was used for all analyses. Comparisons between measures of adherence were done using nonparametric analyses using the Wilcoxon rank sum test. Nonparametric tests were required because the adherence data was skewed.

Results

The demographics of DFMO Study participants are presented in Table 1. The majority of participants were white, non-Hispanic males, with a mean age of ~65. There were no significant differences in baseline demographics between study groups.

One-inch Measured Weights. Gold standard 1-in. weights for each agent are shown in Table 2 (expected daily use). Table 3 displays the study participant's average daily use of each medication based upon weight of returned medication. The greater variability of DFMO is likely due to the consistency of the cream, which caused it to occasionally spurt from the tube.

Overall Adherence. Summary data for medication weight and study diary adherence for each agent are presented in Table 3. Study visits were collapsed for the purpose of analyzing this data. As shown in Fig. 1, medication weight adherence was approximately normally distributed, with 10.2% of participant study visits demonstrating 100% or greater adherence for DFMO. In comparison, self-reported adherence data from the study diary is skewed to the right, with most participant study visits for DFMO (59.2%) showing 100% adherence to the study agents. This distribution was consistent for all agents used in this trial. When variability is taken into account (e.g., all participants within 1 SD of the gold standard are considered adherent), 88.9%, 75.1%, 52.5% and 61.8% of all participant visits show adherence to DFMO, DFMO placebo, triamcinolone, and triamcinolone placebo, respectively.

Adherence Over Time. Figure 2 shows the pattern of adherence over time (months 1-6 of the evaluation period) on this trial for both medication weight and study diary

Table 1. Demographics of study participants

	Treatment group (<i>n</i> = 124)			
	DFMO + triamcinolone (<i>n</i> = 34)	DFMO + placebo (<i>n</i> = 31)	Placebo + triamcinolone (<i>n</i> = 31)	Placebo + placebo (<i>n</i> = 28)
Age, mean (SD)	64.6 (13.3)	64.4 (9.2)	62.8 (10.3)	65.1 (12.4)
Range	40-86	48-80	43-79	35-86
Male, <i>n</i> (%)	28 (82.4)	24 (77.4)	24 (77.4)	24 (85.7)
White, non-Hispanic, <i>n</i> (%)	33 (97.1)	30 (96.8)	30 (96.8)	27 (96.4)
Education				
High school or less, <i>n</i> (%)	8 (23.5)	4 (12.9)	2 (6.5)	7 (25.0)
Some college/trade, <i>n</i> (%)	10 (29.4)	16 (51.6)	19 (61.3)	11 (39.3)
College graduate, <i>n</i> (%)	16 (47.1)	11 (35.5)	10 (32.3)	10 (35.7)

adherence. Both measures of adherence show little variation over time. The occurrence of nonreturned medication or study diaries was very low. One participant randomized to the triamcinolone plus placebo group, and one participant randomized to the double placebo group did not return either study medication or a study calendar at one visit. One participant randomized to the triamcinolone plus placebo group did not return the placebo tubes at one visit (although the triamcinolone tube was returned), and one participant randomized to the double placebo group did not return the triamcinolone placebo tubes at one visit (although the DFMO placebo tubes were returned). These four study visits represent <1% of all study visits. For the analysis over time, interim study visits (e.g., if a participant scheduled additional visits between the routine monthly clinic visits) were not included.

Comparison of Measures. There were statistically significant differences between study diary and medication weight adherence for each agent ($P < 0.001$) using the Wilcoxon rank sum test. Study diary adherence was greater than the medication weight adherence (positive rank) in 1,287 out of 1,509 cases (85.3%).

Discussion

In this study, both self-reported diary records and weight of medication tubes were used to monitor adherence. Most participants (59.2% of all visits) recorded 100% adherence on the study diary; however, using the weight adherence, only for 10.2% of visits were participants completely adherent to the study regimen. This confirms statements in previous publications, that those who self-report being adherent to a medication regimen may not truly be adherent (3, 6, 7). Furthermore, the amount of overestimation from self-report of adherence may be larger than previously thought. In this study, the mean overestimation for the use of each agent was 25.2%, 12.15%, 25.87%, and 29.01% for DFMO, DFMO placebo, triamcinolone, and triamcinolone placebo, respectively. In this study, it is impossible to differentiate between participants who applied less than the recommended 1 in. amount of the agent daily and those who applied the correct amount on a less than daily schedule; therefore, the exact nature of the lack of adherence (daily use/non-use versus daily quantity of use) remains unknown. However, when adherence is assessed based on use within 1 SD of the gold standard measure to take variability of daily use into account, adherence remains low for all agents.

Table 2. Gold standard daily medication weight (in grams)

Medication	<i>n</i>	Mean (SD)
DFMO	30	0.560 (0.313)
DFMO placebo	30	0.480 (0.173)
Triamcinolone	30	0.517 (0.170)
Triamcinolone placebo	30	0.453 (0.189)

Only use of DFMO shows >80% adherence, most likely due to the greater SD of the gold standard for that agent.

Poor adherence can affect the validity of a clinical trial—the cause of a negative outcome could be due to poor adherence rather than the lack of effect of the therapy being evaluated (8, 9), thereby reducing the ability to detect a difference between treatment arms (10, 11). For these reasons, poor adherence or nonadherence may significantly distort the results of a clinical trial and could lead to an increased risk of making a type II error (12). Furthermore, if participants overdose by applying more than the requested amount of medication, other problems may result, such as increased toxicity that may not have occurred at the recommended dosage.

If adherence is measured accurately, the amount of non-adherence can be factored into an analysis, or study methods can be modified to enhance adherence. In the case of inaccurate adherence measurement, study findings may be invalidated and can contribute to a lack of reproducibility in findings. In this study, despite not knowing if lack of adherence was due to consistency or quantity, an adherence value (percentage of recommended use) per participant at each study visit was obtained, making it possible to make these adjustments. Adherence assessment is an extremely important factor in determining the quality of results from any research study involving an intervention and it is essential that it be measured accurately. It is of particular importance to look closely at negative studies that also have a significant number of low adherence values. Analysis of data from clinical trials must take into account the extent of nonadherence when determining study outcomes. However, the quality or calculation of the measure of adherence is only rarely taken into consideration when designing clinical trials or reporting study results.

The greatest risk with medication weight measures, similar to the weaknesses with capsule or tablet count measures, is the inability to calculate adherence if participants do not return all unused study medication or an overestimation of adherence if medication is disposed by the participant. The use of blister packs may reduce the risk of overestimation because a participant must punch out each dose. When medication is packaged in a tube (topical agents) or in a single bottle, and the participant is given more medication than needed for one visit, it is less likely that unused doses will be disposed. However, when bottles or tubes are not returned, adherence cannot be calculated. This may increase the amount of missing data; however, in this trial, <1% of data was missing due to unreturned medication vessels.

The self-report study diary may overestimate adherence because of two primary reasons: (a) participants may miss applications but report daily use (social desirability bias), and (b) participants may be adherent to daily medications but apply less than the recommended quantity of agent. Newer, electronic methods of self-report include handheld diaries. These tools enable investigators to set an alarm that can be used to remind participants to apply topical medications and can be programmed to prevent participants from entering

Table 3. Adherence to DFMO, triamcinolone, and placebo (including interim visits)

Medication	n*	Mean daily medication use in grams (SD)	Mean medication weight adherence, % (SD)	Mean self-reported adherence, % (SD)
DFMO	407	0.399 (0.138)	71.30 (24.69)	96.49 (5.98)
DFMO placebo	350	0.396 (0.121)	82.44 (25.18)	94.58 (12.21) [†]
Triamcinolone	402	0.359 (0.120)	69.45 (23.22)	95.32 (11.11)
Triamcinolone placebo	351	0.303 (0.113)	66.82 (24.88)	95.83 (8.05) [‡]

*Number of study visits measured to obtain mean daily medication use and mean adherence.

[†]n = 351.

[‡]n = 352.

medication use history just before they return for the next clinic visit. However, participants not comfortable or familiar with computer or palm devices may have some difficulty using them. Despite its limitations, a study diary is a valuable tool for participant use beyond simply tracking adherence. They can be used to record adverse events or other symptoms experienced during treatment with a topical agent. In addition, this written diary record can be very useful to help recall and identify potential problems during the study.

Results from this study show that dispensed and returned agent weight is an inexpensive and effective method to measure participant adherence in clinical trials evaluating topically administered chemoprevention agents. The primary weakness in measuring adherence in topical agent studies is

that participants may use the agent, but apply varying amounts, resulting in over- and under-adherence despite daily use. Nevertheless, adding an adherence calculation using medication weight at each clinic visit could address either problem prior to final analysis and may help to reduce nonadherence to the application of study medication and provides an objective measure of adherence that may be used to assess response to the study treatment. Medication weight is a method that could also be applied to studies of oral agents. It is a much less costly and more efficient adherence measure than capsule count due to the packaging requirements (e.g., blister pack versus bottle) and to the effort required to evaluate quantity of returned medication (e.g., counting individual pills versus comparing dispensed and returned medication vessel weight). It is easily incorporated into clinical trials.

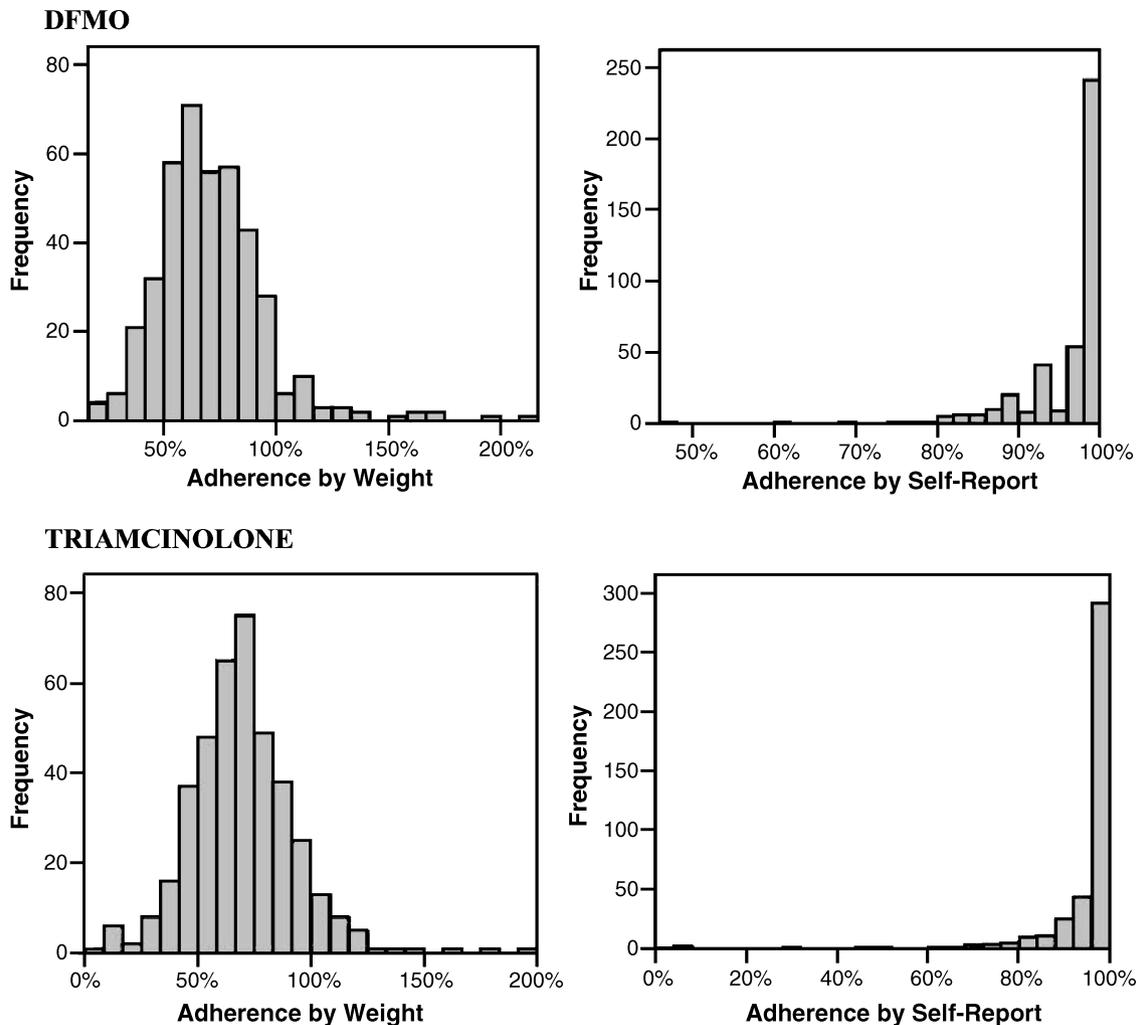


Figure 1. DFMO (n = 407 participant visits) and triamcinolone (n = 402 participant visits) medication weight (left) and study diary (right) adherence histograms.

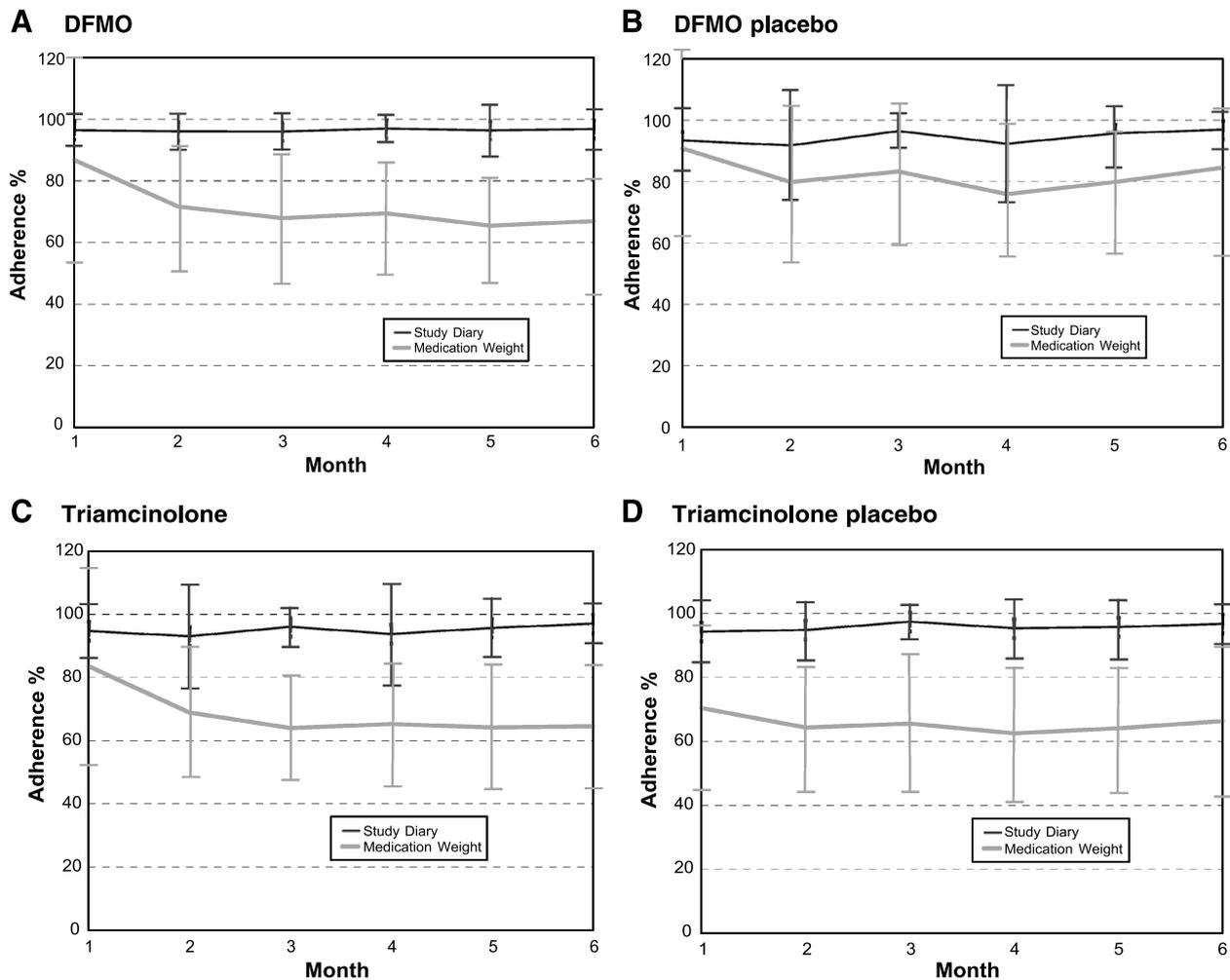


Figure 2. Mean participant adherence \pm 1 SD for (A) DFMO ($n = 369$ total participant visits); (B) DFMO placebo ($n = 323$); (C) triamcinolone ($n = 369$); and (D) triamcinolone placebo ($n = 323$) by study visit.

Returned medication weight adherence is of high value in a trial of topical agents due to the fact that it is an objective, quantitative and direct measure of adherence. There was a wide range of medication weight adherence to topical agents in this trial (13-546%), which suggests it would be of value to make use of metered dosing applicators to ensure accurate dispensation of daily doses. Furthermore, if a participant was placed on a reduced dosage (e.g., for toxicity or for a small individual), the amount used could also be standardized.

Returned medication weight adherence is also quite suited for use in capsule trials, where the amount used per day (e.g., one capsule) does not involve daily inter- or intrasubject variation as does topical agent application. In the case of tablets or capsules, the gold standard should have a SD of zero. Future work should further evaluate the feasibility, acceptance, and validity of this method in trials of oral and topical agents.

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