Received: 25 April 2017 | Revised: 7 September 2017 | Accepted: 13 September 2017

DOI: 10.1002/pds.4331

WILEY

REVIEW

Challenges of post-authorization safety studies: Lessons learned and results of a French study of fentanyl buccal tablet

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Abstract

Purpose: Recruiting and retaining participants in real-world studies that collect primary data are challenging. This article illustrates these challenges using a post-authorization safety study (PASS) to assess adverse events (AEs) experienced with fentanyl buccal tablet (FBT) over 3 months of treatment.

Methods: This was an observational, prospective, multicenter study in France conducted over 1 year. The study employed primary data collection in FBT-treated patients and their treating physicians via a site qualification questionnaire and patient log completed by physicians and a questionnaire and pain diary completed by patients. Strategies to increase participation included reminders, newsletters, frequent follow-up telephone calls, and reducing the extent of data collected.

Results: Of the 1118 physicians contacted who returned the participation form or responded to a telephone call, only 128 expressed willingness to participate. Key reasons for non-participation were lack of interest (69.7%) and FBT not being used in practice by the contacted physician (25.1%). Overall, 224 patients were screened by 31 physicians, and 97 were enrolled. Key reasons for patient non-inclusion were unwillingness or inability to complete the patient AE diary or questionnaire (40.9% [52/127]) and patients' decision (33.9% [43/127]).

Conclusions: Despite efforts to increase participation, enrollment in this study was low. Recruitment and retention methods are limited in their capacity to optimally execute a primary data collection in a PASS. For a PASS to provide reliable and valid information on medication use, involvement from health care agencies, regulators, and pharmaceutical companies is needed to establish their importance, drive study participation, and reduce patient withdrawal.

KEYWORDS

patient selection, postmarketing, product surveillance, safety

1 | INTRODUCTION

Post-authorization, non-interventional safety or surveillance studies are conducted to gather information on the routine clinical use and real-world safety profile of pharmaceutical products.[1-3] Along with clinical trials, case reports, and spontaneous reporting, these types of studies are integral to the assessment of adverse events (AEs) of marketed medications.[2,4] The primary benefits of an observational post-authorization safety study (PASS) include (1) evaluation of a typically large and heterogeneous population of patients receiving usual clinical care, including those receiving the drug for off-label conditions[1,2,4] and (2) evaluation of product use patterns, such as adherence and compliance with approved drug use.[2,4,5]

PASS investigations are typically designed as non-interventional, observational investigations in which patients receive routine clinical care.[2,6] As these studies are non-randomized in design, they may suffer from inherent biases, such as selection bias and confounding. In addition, an observational PASS that involves primary data collection may suffer from insufficient recruitment and participation, particularly when drug use is low. Unlike clinical trials, PASSs generally do not involve a clinical incentive for patients to participate. These studies do not offer treatment with experimental medications, nor do they allow patients to receive additional clinical care, such as further tests, examinations, or unscheduled medical visits. In addition, studies involving off-label use of medications also have the potential to deter

physician participation. Such conditions may contribute to low interest in study participation by patients, resulting in low recruitment, loss to follow-up, and early withdrawal. Moreover, because these studies are performed in a real-world setting, they often target routine clinical practice physicians, who are not involved in clinical research as part of their daily practices and may not be interested in study participation.

The challenges of recruitment and participation in observational studies that involve primary data collection necessitate the use of motivating factors different from those used in clinical trials.[1]

This article discusses the challenges and limitations of PASS investigations and describes strategies undertaken to address these challenges. These issues will be addressed in the context of a study conducted to monitor the safety of fentanyl buccal tablet (FBT).

KEY POINTS

- A post-authorization safety study of fentanyl buccal tablet in France encompassed key challenges associated with observational studies and offers practical implications for future investigations.
- Key challenges in observational post-authorization safety studies involving primary data collection include recruiting and retaining physicians and patients in a study without a clinical incentive and overcoming confounding factors such as concomitant diseases and medications.
- Involvement and cooperation of health care agencies, regulators, and pharmaceutical companies when conducting post-authorization safety studies are essential to create recognition of the importance of these studies, drive recruitment, and reduce patient withdrawal.

2 | METHODS

2.1 | Post-authorization safety study of fentanyl buccal tablet

The safety of FBT (Effentora®; Teva Pharmaceutical Industries Ltd., Frazer, PA, USA) was evaluated in a PASS conducted in France, primarily to estimate rates of AEs over the first 3 months of treatment in a real-world setting. Other study objectives included elucidating FBT treatment patterns and evaluating physician and patient satisfaction with educational materials (ie, patient education brochure, health care professional guide, and titration tool) that are part of a European Risk Management Plan for FBT. FBT is a rapidly dissolving opioid formulation that enhances fentanyl transmucosal absorption and bypasses first-pass metabolism.[7,8] FBT is approved in the United States and European Union for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving opioid maintenance therapy for chronic cancer pain (ie, opioid-tolerant patients).[9,10] FBT requires dose titration to provide adequate pain relief and minimize AEs; the initial 100-μg dose can be titrated upward, as necessary, through the range of available tablet strengths (100, 200, 400, 600, and 800 μg).[10]

2.2 | Study design and procedures

2.2.1 | Study enrollment

The study was designed as an observational, prospective, multicenter PASS in France. Recruitment began in January 2013 and was carried out for 1 year. The group of physicians identified by the sponsor as likely to prescribe FBT that was contacted and invited to participate in the study comprised 1589 general practitioners and specialists (Figure 1). Efforts to increase participation included communication with physicians by the sponsor's medical scientific liaisons to raise awareness of the study. This communication was carried out through multiple channels, including by telephone, in writing, and in person, and included regular newsletters to physicians and more frequent follow-up telephone calls. Patients were also contacted by telephone to encourage participation. Despite these efforts, physician enrollment was low, and as a result, recruitment was stopped after 97 patients were enrolled by 31 physicians over a 12-month period.

Patients were eligible for enrollment if they were naïve to FBT and were to start FBT titration as part of their routine clinical care. Patients were excluded if they were under legal guardianship or participated in any clinical trial within 30 days of study drug administration. All participants provided written informed consent, and they (or their caregivers) had to be able and willing to complete an AE diary and

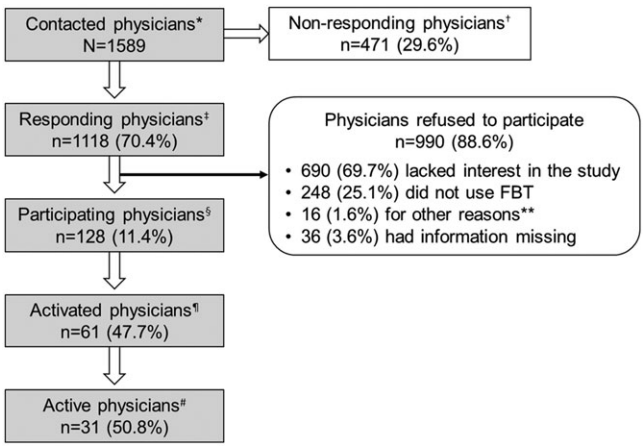

FIGURE 1 Physician recruitment and participation. *Physicians for whom a contact letter was sent. †Physicians who did not return their participation form and/or who were not reachable by telephone. ‡All contacted physicians who returned their participation form or who were reached by telephone. §Physicians who accepted to participate in the study via the participation form or by telephone. ¶Physicians who accepted to participate and signed the financial agreement. #Physicians who reported ≥1 patient in the patient log or in the case report form. **Other reasons for 16 physicians: 3 were participating in competitive or different studies; 3 were leaving the investigational site; 2 did not want to answer the phone about studies; 2 for personal reasons; 1 would re-contact if interested after reading documentation; 1 did not treat pain; 1 refused to participate; 1 only participates in studies related to nutrition; 1 refused to provide a reason for not participating; and 1 refused because of conflict of interest

patient questionnaire. The PASS protocol was approved by the French National Agency for Medicines and Health Products Safety.

2.3 | Data collection and analysis

Physicians completed a site qualification questionnaire (SQQ), which included information regarding age, gender, specialty, department of practice, type of activity, institution type, and reason for non-participation. In addition, they completed a patient log that included patient demographics as well as information regarding the reason for exclusion from the study. At the start of follow-up, physicians provided baseline information for participating patients, including demographics, Eastern Cooperative Oncology Group performance status, medical history including the cause of pain and history of BTP episodes over the preceding 15 days, and concomitant diseases and medications. Patients completed a questionnaire regarding their history of substance abuse, as well as a pain inventory. Information on the presence of symptoms resembling FBT AEs (eg, nausea, vomiting, constipation, dizziness) was collected before patients were initiated on FBT. FBT dosage and treatment were recorded in patient diaries at inclusion and during a 3-month follow-up visit. All reported AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v15.0. Physicians assessed the seriousness and relatedness of AEs. Relatedness was categorized as "no reasonable possibility" or "reasonable possibility" based on temporal sequence between drug administration and AE, patient's clinical state, known pattern of response to FBT, and response to cessation/re-initiation of FBT. Physicians and patients also rated their satisfaction with the FBT educational materials.

In addition to the data gathered on drug use and AEs, information on the characteristics of participating and non-participating physicians and patients was collected from the SQQ and patient log, respectively, to assess selection bias. To control information bias, data quality control visits were conducted on a 10% sample of physicians with the highest number of recruited patients to determine how closely their medical record data matched the information provided in the case report forms.

The analysis of study results was mainly descriptive. A sensitivity analysis was conducted using data from patients who had a delay of >2 weeks between their last FBT intake and follow-up visit to address recall bias and to assess the real occurrence of AEs during treatment. Patients who discontinued FBT before the end of the 3-month follow-up period were considered withdrawn from the study.

3 | RESULTS

3.1 | Description of study participants

A total of 1589 physicians were contacted, and 1118 (70.4%) returned the participation form or responded to a telephone call (Figure 1). Of the 1118 physicians, only 128 (11.4%) expressed willingness to participate, of which 25.9% were general practitioners and 74.1% were specialists (eg, oncology, pain management). The main reasons for non-participation were lack of interest in the study (69.7% [690/990]) and FBT not being used in practice by the contacted physician (25.1% [248/990]). The mean (standard deviation [SD]) age of participating physicians was 46.0 (8.6) years, and the majority (62.4%) were men. Of the 128 physicians, 31 (24.2%) registered ≥1 patient and were considered active study physicians.

Overall, 224 patients were screened by the 31 physicians, and 97 were ultimately enrolled in the study. The main reasons for non-inclusion of 127 patients were unwillingness or inability to complete the patient AE diary or questionnaire (40.9% [52/127]) and patients' decision (33.9% [43/127]); other reasons included investigators' decision (16.5% [21/127]), other medical conditions (3.9% [5/127]), worsening of underlying condition (2.4% [3/127]), enrollment in another study (1.6% [2/127]), and patient age under 18 years (0.8% [1/127]). Of the 97 enrolled patients, 7 did not receive any dose of FBT, making the final analysis population 90 patients.

Demographic and baseline characteristics of the study population are provided in Table 1. The occurrence of breakthrough cancer pain (BTcP) over the 15 days preceding enrollment was reported in 85 of the 90 (94.4%) patients, with a mean of 4.4 (SD: 2.5) episodes per day during this period. Almost all patients (97.8% [88/90]) received concomitant pain medications during or after planned FBT initiation, and 71.1% (64/90) adjusted or stopped ≥1 pain medication other than FBT (Table 2). In total, 82.2% (74/90) of patients prematurely withdrew from the study. The most common reasons for withdrawal were AEs (41.1% [30/73]), treatment no longer required (20.5% [15/73]), death (16.4% [12/73]), lack of efficacy (13.7% [10/73]), patient withdrew consent (1.4% [1/73]), and other (6.8% [5/73]); reason for withdrawal was missing for 1 patient.

Most patients (84.4% [76/90]) received FBT 100 μg per BTP episode, which is the initial recommended dose. A successful dose, defined as the dose that provided adequate analgesia and minimized undesirable effects, was reached by 59.6% (53/89) patients and ranged from 100 to 800 μg per BTP episode. For 52.8% (28/53) of patients, the successful dose was 100 μg per BTP episode.

TABLE 1 Demographics and baseline characteristics

Characteristic	Patients (*N* = 90)
Mean (SD) age, years	61.5 (11.3)
Age category, *n* (%)	
<65 years	54 (60.0)
≥65 years	36 (40.0)
Gender, *n* (%)	
Male	43 (47.8)
Female	47 (52.2)
Professional status, *n* (%)	
Employed	22 (24.4)
Unemployed/retired	68 (75.6)
Ambulatory, *n* (%)	64 (71.1)
Inpatient, *n* (%)	26 (28.9)
Type of pain, *n* (%)	
Chronic pain	83 (92.2)
Non-chronic pain	7 (7.8)
Maximum number of BTP episodes per day (mean [SD])	4.4 (2.5)

BTP, breakthrough pain; SD, standard deviation.

TABLE 2 Concomitant pain medications

Previous pain medication	
≥1 previous pain medication, *n* (%)	28 (31.1)
Concomitant pain medication during or after FBT initiation	
≥1 concomitant pain medication, *n* (%)	88 (97.8)
Change in concomitant pain medication during follow-up	
≥1 change in pain medication (other than FBT), *n* (%)	64 (71.1)
≥1 dose adjustment in pain medication (other than FBT), *n* (%)	30 (33.3)
Time to first dose adjustment (days), mean (SD)	40.7 (30.6)
≥1 pain medication stopped (other than FBT), *n* (%)	50 (55.6)
Time to first medication stop (days), mean (SD)	22.1 (28.8)

FBT, fentanyl buccal tablet; SD, standard deviation.

3.2 | Adverse events

AEs at the inclusion visit were considered AEs that occurred before FBT treatment initiation. These pre-FBT AEs were collected to assess the potential confounding of AE association with FBT treatment. AEs collected between the inclusion and follow-up visits (ie, post-FBT initiation) were considered AEs that occurred during titration and stabilization. At inclusion (ie, pre-FBT), ≥1 AE was reported by 54.4% (49/90) of patients; during the 3-month follow-up (ie, post-FBT initiation), ≥1 AE was reported by 82.2% (74/90) of patients. Treatment-related AEs were reported in 47.8% (43/90) of patients, and serious treatment-related AEs were reported in 10.0% (9/90) of patients. At follow-up, the most frequently reported AEs were nausea (22.2% [20/90]), fatigue (22.2% [20/90]), sedation (21.1% [19/90]), dizziness (17.8% [16/90]), constipation (16.7% [15/90]), headache (12.2% [11/90]), and vomiting (11.1% [10/90]). Patients' Eastern Cooperative Oncology Group performance status worsened over the course of the study. Grade 1 was reported in 44.4% (40/90) of patients at inclusion and 30.0% (27/90) at follow-up, and grade 3 or 4 was reported in 16.7% (15/90) of patients at inclusion and 52.2% (47/90) at follow-up. The rate of hospitalization increased from 28.9% (26/90) at inclusion to 40.0% (36/90) at follow-up. At the end of the 3-month follow-up, treatment with FBT was continued in 20.0% (18/90) of patients. General health deterioration or underlying malignancy contributed substantially to premature discontinuation.

3.3 | Sensitivity analyses

Comparison of participating and non-participating physicians using SQQ data found no meaningful differences between the groups. Overall, the sample of participating physicians closely captured the clinical specialties of those who prescribe FBT. Comparison of included and non-included patients using patient log data also did not reveal meaningful differences in baseline characteristics between the groups. A sensitivity analysis was performed using data from 56 patients who had a delay of >2 weeks between their last FBT intake and follow-up visit. AE rates were similar between the analysis population and the patient subset used in the sensitivity analysis.

3.4 | Satisfaction with educational brochure

Approximately half of enrolled patients (48.9% [44/90]) provided feedback on the FBT educational brochure. Most responding patients (97.6% [40/41]; data missing for 3 patients) received the brochure from their physicians, and 88.1% (37/42; data missing for 2 patients) reported that the physicians explained the contents to them. Of the 73.8% (31/42; data missing for 2 patients) of patients who reported reading the brochure, 96.8% (30/31) indicated that the brochure was clear and comprehensive and 93.5% (29/31) indicated that it was accurate.

Of the 128 participating physicians, 58 (45.3%) provided information on their satisfaction with the health care professional guide and titration tool. Most physicians reported that the guide and tool were clear (98.3% [57/58] and 94.8% [55/58], respectively), accurate (93.1% [54/58] and 98.3% [57/58], respectively), and comprehensive (94.8% [55/58] for both).

4 | DISCUSSION

The observational, prospective, multicenter PASS of FBT in France described here encompassed several key challenges known to be generally associated with observational studies employing a primary data collection. Notably, the recruitment process was hampered by several obstacles, many of which stemmed from the nature of the routine clinical practices involved in the treatment of the FBT primary care population. These factors included limited use of FBT in hospitals, lack of interest to participate in the study, and physicians' difficulty complying with a 3-month follow-up, because patients were typically treated for shorter durations. Additionally, the FBT discontinuation rate was high, as may have been expected, owing to the severity of the patients' underlying disease and the practice of opioid switching and opioid rotation in oncology patients.[11]

The initial pool of contacted physicians consisted of 1589 general practitioners and specialists, including oncologists and pain management physicians. The group was geographically dispersed and included a wide representation of clinical settings. This pool of potential participants was theoretically large enough to allow randomized or specialty-weighted sampling of the physicians participating in the study. In reality, the response rate from this population was extremely low, with only 8.1% (128 physicians) of the pool agreeing to participate in the study and only 2.0% (31 physicians) eventually enrolling patients in the study. The low rate of participation was similar to that observed by Ayres et al in a PASS of a non-chlorofluorocarbon metered-dose inhaler, in which only 646 of 11,300 (5.7%) general practitioners agreed to participate and recruited patients.[12] Key factors cited by physicians as barriers to participation in clinical trials included lack of time and resources.[13] In a survey of US and European physicians, 70% indicated that current regulations make clinical trials difficult to

manage.[14] Moreover, in the United Kingdom from 1994 to 2002, fewer than one third of funded studies achieved recruitment targets.[15]

In the current FBT study, recruitment and retention efforts were performed both to overcome the low response rate in the initial recruitment of the study population and to increase compliance with data collection. To overcome the low response rate, non-responding physicians were contacted by study representatives. The sponsor's medical scientific liaisons provided necessary information about FBT to physicians and explained the clinical relevance and necessity of the PASS. These communication tools were consistent with the various motivating factors used for observational studies, as previously reported by Kiri et al and Rahman et al.[1,13] To increase patient enrollment, reminders and newsletters regarding the recruitment of patients to the FBT study were sent to the participating physicians and the frequency of initially planned follow-up telephone calls was increased. To decrease the number of patients lost to follow-up, all ambulatory patients and caregivers were contacted by telephone to complete patient diaries. Study physicians were requested to contact family doctors to obtain information in case an ambulatory patient died.

In our study, recruitment was focused on physicians, and there was no direct advertisement to patients (eg, newspaper, social media), which has been shown to be effective.[16,17] However, the success of advertising is highly dependent on the study design and patient population. In a study of patients older than 60 years of age who were prescribed a regular nonsteroidal anti-inflammatory drug, the response rate from newspaper advertisements was only 4.7%. The most effective advertising methods include multiple delivery devices, but cost-effectiveness of these different methods is highly variable.[16,18]

In our study, despite including strategies to improve participation and retention in the study methodology, the response rate among the physicians remained low and resulted in a limited final sample size. This finding highlights the need for additional approaches to improve physician and patient recruitment. Health care agencies and regulators, along with pharmaceutical companies, need to encourage participation by raising awareness of the important goals of clinical research.[13] Removing barriers to clinical research is equally important. The most commonly reported obstacles in clinical research are insufficient funding, the need for well-trained clinical investigators, and the lack of enhanced information systems to identify clinical trials and assist physicians in understanding regulatory requirements, liability, and compensation.[13,14,19] The European Network of Centers for Pharmacoepidemiology and Pharmacovigilance is a network of public institutions and contract research organizations coordinated by the European Medicines Agency to facilitate the conduct of PASSs and provide guidance on study design, data sources, and analysis.[1,20] From the health care organization perspective, the National Institute of Mental Health published a list of points to consider for recruitment and retention in clinical research studies, which include suggestions to work with local community organizations, conduct pilot tests of recruitment strategies, and encourage patient retention with small tokens of appreciation.[21]

In addition to limiting the sample size, non-participation and lack of randomization in PASSs may result in selection bias, limit statistical power, and reduce external validity.[1,3,13] In an attempt to estimate the magnitude of selection bias, several steps were taken in the FBT study design. First, a comparison of the baseline characteristics of participating and non-participating physicians and patients was undertaken, and no meaningful differences between the groups were identified. Second, AE analyses stratified by patients' demographic and clinical characteristics were included in the design; however, because of the small sample size, these analyses could not be conducted.

A stratified AE analysis could have determined factors relevant to confounding by indication, which can also be a major challenge in observational studies.[1,6,22] In the population studied here, the main contributors to AEs were likely the type and stage of cancer and type and timing of treatment. Given the fact that many of the participants were late-stage oncology patients, the comorbidity load and rate of polypharmacy were both high and increased as the study progressed. Use of concomitant pain medications increased substantially from 31.1% before enrollment to 97.8% during the study and after FBT initiation. Additionally, the majority of patients modified the dose of their concomitant pain medications. Frequent medication adjustments, such as opioid rotation and combination treatment strategies, are characteristic of cancer pain management.[11] In addition, the results of the FBT study demonstrated a substantial increase in the rate of inpatient hospitalizations and worsening of the Eastern Cooperative Oncology Group performance status over the course of the study.

Because of the nature of observational design, some data elements could not be collected in sufficient clinical details. Specifically, to avoid cumbersome data collection, which would have significantly reduced compliance with the study protocol among the largely research-naïve physicians, the burden of questions was reduced compared with the extent of data collection in randomized controlled trials. For example, the design of the FBT study did not include data collection related to exact timing of AEs relative to FBT intake, number of BTcP episodes during follow-up, severity and duration of AEs, and duration of time between cancer diagnosis and occurrence of AEs, which may have confounded the association between FBT and AE occurrence. Baseline (ie, pre-FBT) frequencies of AEs at the inclusion visit were collected at enrollment to address and minimize this potential confounding. However, the rate and type of AEs could not be adjusted to the increasing comorbidities load and changes in concomitant medications over the course of the study, owing to the small sample size. Accordingly, a conservative approach was undertaken, and all reported events were included in this study. In addition, a delay was observed for a subset of patients between the last FBT intake and the follow-up visit, during which AEs were collected. A sensitivity analysis, which was intended to examine the effect of this gap between treatment timing and AE reporting, determined that there was no effect of this delay on AE reporting.

5 | CONCLUSIONS

Despite the numerous outreach attempts, including those described in professional literature as effective measures of study recruitment and retention, the FBT PASS was limited by low enrollment. The primary reasons for non-participation were lack of interest and limited use of FBT in practice. However, for the 90 participants, the AE profile

of FBT was consistent with that found in prior reports,[9,10,23-26] and no new safety signals were identified.

The experience from the FBT study offers practical implications for future PASS investigations. Health care agencies and regulators, along with pharmaceutical personnel, need to be aware of the challenges and limitations of real-world investigations of drug utilization, especially when assessing off-label use. Key considerations include methods of recruiting physicians and retaining patients in a study without a clinical incentive, as well as overcoming confounding factors in patients with significant concomitant diseases and medications. In addition to the study recruitment efforts performed by the pharmaceutical companies, the involvement of other health care organizations is important for raising the awareness of PASS investigations, especially among the physicians working in routine clinical practice.

ACKNOWLEDGEMENTS

The authors would like to express their appreciation to Philippe Huot-Marchand from Real World Evidence, Mapi Group, Lyon, France, for his contributions to and involvement in the study.

FUNDING

This study was sponsored by Cephalon, Inc., now a wholly owned subsidiary of Teva Branded Pharmaceutical Products R & D, Inc. (Frazer, PA, USA). Writing support was provided by Bina J. Patel, PharmD, CMPP, of Peloton Advantage, LLC, funded by Teva Branded Pharmaceutical Products R & D, Inc. Teva provided a full review of the article.

TRIAL REGISTRATION

The study was registered in the EU PAS Register under the number EUPAS10402.

CONFLICT OF INTEREST

Natalie Gavrielov-Yusim and **Ilda Bidollari** were employees at Teva Pharmaceuticals, and may or may not have owned stock options at the time of study conduct and manuscript preparation. **Netta Bartov** and **Sigal Kaplan** are employees of Teva Pharmaceutical Industries Ltd.

ETHICS STATEMENT

All procedures performed in this study involving human participants were in accordance with the Good Epidemiology Practice guidelines, the ethical principles arising from the Declaration of Helsinki revised in 1989, and all current local regulations.

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How to cite this article: Gavrielov-Yusim N, Bidollari I, Kaplan S, Bartov N. Challenges of post-authorization safety studies: Lessons learned and results of a French study of fentanyl buccal tablet. *Pharmacoepidemiol Drug Saf*. 2018;27:457–463. https://doi.org/10.1002/pds.4331