ADDICTION 'FOR DEBATE'

Post-Marketing Studies of Pharmaceutical Opioid Abuse-Deterrent Formulations: A Framework for

Research Design and Reporting

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Abstract

Background and aims: Opioid formulations with properties to deter abuse (abuse-deterrent formulations; ADFs) have been developed as one response to the prescription opioid 'epidemic'. As for all medicines, ADFs undergo evaluation of safety and efficacy prior to registration for marketing. Yet, reduced extra-medical use (the primary intended outcome of ADFs and reason for their introduction) can only be established in post-marketing observational studies, comparing them to opioid formulations without abuse-deterrent properties. This has implications for various features of study design and analysis. We discuss proposals for the design, conduct, governance, and reporting of post-marketing studies on the effectiveness of pharmaceutical and opioid ADFs.

Methods: A review of current guidance documents, public workshops and forums, and our own experience with post-marketing studies of ADFs.

Results/Conclusions: Research questions for post-marketing studies on abuse-deterrent formulations (ADFs) of opioids should reasonably be framed around detecting *any* likely intended or unintended clinical and/or meaningful changes in specific aspects of extra-medical use (e.g., injection use) and harms. Outcomes reported by prevalence and frequency of occurrence and disaggregated by specific product and route of administration can illustrate magnitude of ADF impact. We argue that a multi-faceted approach is required, using data from both general population and sentinel high-risk cohorts, and from primary and secondary data sources. The comparator (historical non-ADF formulation of that opioid, equivalent current generic or similar opioid product), duration of monitoring, and analytical approach require justification and should be sufficient to add weight to conclusions of causality. To maximise transparency, we recommend explicit declarations of funding and conflict of interest, establishment of an advisory committee, publication of study protocol, and access to all study results.

INTRODUCTION

Pharmaceutical opioid use carries a risk of dependence, and this risk is increased when pharmaceutical opioids are used extra-medically (i.e., outside of a medical professional's advice; 1). Development of abuse-deterrent formulations (ADFs) of pharmaceutical opioids is one response to increased pharmaceutical opioid extra-medical use and harms in North America (2, 3). The primary intent of ADFs is to reduce specific aspects of extra-medical use by targeting certain behaviours, such as tampering and use via routes of administration other than as intended (e.g., crushing to snort or inject tablet formulations intended for oral consumption).

Definition and Mechanisms of ADFs

ADFs make these behaviours less rewarding or more difficult through:

1. physical or chemical barriers (e.g., formulations containing hydrogelling agents which resist crushing or dissolving);
2. antagonist/agonist combinations (e.g., opioids with corresponding antagonist such as naloxone or naltrexone released on tampering);
3. specific delivery systems (e.g., opioid implants or depot injections);
4. prodrugs (e.g., opioid released after parent drug ingested and metabolised through stomach enzyme, i.e., orally); and/or
5. aversive components (e.g., aversive agent like sodium lauryl sulfate released on tampering) (4).

Abuse deterrence does not infer complete prevention of extra-medical use and ADFs are unlikely to deter the most common form of extra-medical use, where opioids are used via the intended route of administration but in excess of the prescribed dose (4, 5). Thus, ADFs form one strategy in what needs to be a multifaceted response targeted at curbing pharmaceutical opioid use and harms (6). Indeed, each ADF must be individually evaluated in terms of risk-benefit, reinforced by recent removal from the market of reformulated products with ADF properties with insufficient evidence to support ADF labelling, and post-marketing data indicating greater harms from extra-medical use (7). Critical to evaluating the possible role of ADFs as part of this response is having high-quality robust

data regarding the nature and extent of impact these formulations have in reducing extra-medical use and associated harms.

Contemporary Post-Marketing Surveillance and ADFs

Like any prescribed medicine, ADFs must undergo post-marketing assessment. Traditional post-marketing surveillance of activities focus on pharmacovigilance: safety as typically assessed by adverse event reporting (8). Although safety remains a primary concern, there is increasing recognition that passive systems of adverse event detection (like adverse event reporting) fall short, in that they do not have the capacity to quantify the true magnitude of risk from a particular medicine (9). Contemporary systems that harness administrative and other sources of data (e.g., prescription monitoring programs, analyses of administrative and other data) have the capacity to quantify risk, with certain regulatory bodies (e.g., the US Food and Drug Administration; FDA) requiring active and extensive monitoring of outcomes after the medicine is approved for marketing (10).

Unlike other medicines, ADFs are developed specifically to minimise unintended patterns of opioid use that are known to be harmful. Randomised controlled trials can establish pharmaceutical opioid safety and efficacy. Yet, the latter is limited to the assessment of the pharmacological impact of the opioid. Reductions in extra-medical use associated with a specific formulation can only be established in post-marketing observational studies and require comparison to opioid formulations without abuse-deterrent properties. This also has implications for the design and conduct of ADF post-marketing studies.

Current Post-Marketing Surveillance Guidance for ADFs

To our knowledge, only the US has a regulatory framework regarding the level of pre- and post-marketing evidence required for industry to label a product as an ADF (4). Two major documents provide guidance: the FDA guidance (4) and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), written by a group comprising representatives from government organisations, pharmaceutical companies and research organisations (11). Both sources outline recommendations for study design. However, neither addresses issues around study

conduct, governance, and reporting. This issue is particularly pertinent given the need for rigorous review of evidence used to inform medicine regulation, and emphasis on transparency and reproducibility of findings.

‘For Debate’ Objectives and Sources of Information

In this ‘For Debate’ piece, we examine the complexities of this issue, proposing a framework for study design, conduct, governance, and reporting of pharmaceutical opioid ADF post-marketing studies. ADFs are a relatively new strategy (the US FDA has approved labelling describing abuse-deterrent properties for eight opioids, including oxycodone and morphine formulations; 12), and there has been substantial maturing of this field of research in the wealth and quality of studies conducted (13-31). Yet, the opportunities for new developments are great, and there is growing momentum for more comprehensive guidance for such studies. This call for further guidance is also driven by government regulators charged with making decisions regarding product registration and public subsidy (10, 32, 33), and heightened by the withdrawal of ADFs from the market based on post-marketing evidence of increased harms (7, 34). Thus, the discussion outlined in this manuscript is timely, and integral to the shaping of this field of research moving forward. Prior and current post-marketing studies may use some components of the suggestions below, but we believe it is important to synthesise current viewpoints and provide clarity in highlighting the best approaches for the field into the future.

The proposals we make here draw upon the existing guidance noted above (4, 11), public workshops and forums on opioid ADFs (35), discussions of transparency for pharmaceutical clinical trials and observational studies (36), and our own experience conducting post-marketing studies of pharmaceutical opioid ADFs (20, 37-39). We also summarise key features of post-marketing studies of ADFs identified in a recent systematic review of ADF effectiveness and value (5), which is available online in full (<https://icer-review.org/announcements/final-adf-report/>). Our commentary does not cover all aspects of the research process; instead, we have focused on the domains related to study design, conduct, and reporting where guidance and standards are being debated in the aforementioned contexts.

ADF POST-MARKETING STUDY DESIGN COMPONENTS

ADF Post-Marketing Study Research Question

Post-marketing studies of pharmaceutical opioid ADFs assess whether an ADF results in meaningful changes in extra-medical use and harms. Given the intent of ADFs, the research questions and hypotheses might reasonably be framed around detecting a reduction in specific practices, such as insufflation or injection, other aspects of extra-medical use (e.g., attractiveness in the illicit opioid market), and harms (4). Some studies have identified the intended consequence of ADF introduction (i.e., lower levels of tampering with the ADF relative to the comparator) coupled with unintended consequences (e.g., switching to extra-medical use of other pharmaceutical opioids and/or heroin use; 5). Consequently, it may be appropriate to operationalise the research question to detect *any* likely intended or unintended clinical and/or practically significant changes associated with ADF introduction (i.e. an increase or decrease in these indicators, not necessarily restricted to the use and harms of the ADF product itself).

Outcomes

As aforementioned, the core outcome of post-marketing studies comprises the patterns of opioid use targeted by the ADF, yet other aspects of extra-medical use and harms are also important to monitor for demonstrating both ADF effectiveness and safety (for elaboration, see **Figure 1**). In terms of monitoring broader unintended consequences of ADFs, we argue that post-marketing studies should also measure total population-level opioid exposure given possible changes in overall utilisation, and market features (e.g., street price) given the association with rates of extra-medical use and harms (5, 40). These outcomes can be split into various facets (see **Figure 1**). Each of these can contribute to evidence regarding ADF impact, and we believe are important in weighing up risk and benefit (4, 11).

Figure 1 here

The outcomes specified in **Figure 1** should be disaggregated where possible by: i) the specific ADF and relevant comparators, and ii) use via any route and route-specific (e.g., intravenous versus intranasal use) (4). There may be instances where outcomes cannot be disaggregated by specific product or route of administration, and it may be appropriate to describe data by the smallest

possible unit (e.g., by active ingredient). To illustrate magnitude of ADF impact, outcomes can be quantified by their prevalence and frequency of occurrence where possible. This depth of information captures the scale of change associated with the ADF and facilitates comparison to comparator non-ADF formulations.

Design, data sources and populations

Although not an exhaustive list, key study designs for post-marketing studies of pharmaceutical opioids comprise i) *time series*: where exposures and outcomes are observed at multiple time points from the same or different individuals (e.g. the number of prescriptions per month); ii) *cross-sectional*: where exposures and outcomes are collected at a single point in time or serially (not necessarily at equally-spaced intervals) from the same or different individuals (e.g. surveys of people who inject drugs); and iii) *cohort*: where exposures and outcomes are observed across multiple points of time (not necessarily at equally-spaced intervals) from the same individuals (e.g. people prescribed pharmaceutical opioids followed longitudinally). Other study designs (e.g., self-controlled designs) might also be considered (41)

These study designs can utilise different types of data, specifically *primary data* collected and collated for the purpose of the study, or *secondary data* collected for other purposes that can provide information on the key outcomes of interest (typically administrative data, e.g., hospital separations, police drug seizures). They can also use data from different samples: representative of the general population or of sentinel high-risk populations (i.e., a surveillance group in which emerging trends are most likely to be observed). The latter may comprise those populations most likely to engage in extra-medical opioid use, where we are most likely to observe the impacts of ADFs (e.g. people who are opioid-dependent, people who use illicit drugs, people who inject drugs).

Study design, data type and population can determine the degree to which a post-marketing study can: 1) identify events in the total population (signal detection) versus individuals at elevated risk (risk management); 2) identify rare events; 3) detect change in events; 4) identify changes in events at the population- versus individual-level, and 5) provide timely information. In **Table 1**, we provide a matrix of proposals regarding the degree to which these five objectives can be achieved using

various study designs, data types, and populations. Indeed, ADF post-marketing studies have an additional level of complexity given the range of outcomes and levels of disaggregation by product and route of administration, as well as potential jurisdiction-level differences in ADF policy and data availability. Thus, a multi-faceted approach using various study designs, population and sources may be appropriate.

We argue that data may need to be obtained from both general population and sentinel high-risk samples, and from primary and secondary data sources. General population data permit estimates of population level exposures and risks of outcomes; sentinel high-risk population data reflects outcomes in the group at greatest risk of reporting extra-medical use of ADFs or outcomes. Primary data collection can be designed to permit disaggregation by drug, dose, and route, providing detailed pharmaceutical opioid exposure and extra-medical use data. This level of information is typically not available in secondary data. Despite its limitations (42, 43), secondary data (particularly population-wide datasets) are also important to post-marketing studies, having greater capacity to capture rare events relative to primary data. For example, changes in opioid overdose are more likely to be detected in routinely-collected ambulance data than in survey data given the large sample size necessary to detect change in this low incidence event (38). The proposed capacity of various secondary data sources to measure the core outcomes in ADF post-marketing studies is outlined further in **Table 2**.

Table 1 here

In considering a multi-faceted approach to ADF, we highlight two particular combinations of study design, data type, and population: i) *time-series study of the general population using secondary data*; and ii) *cohort study of sentinel high-risk population using primary and/or secondary data* (**Table 1**). Both capture events over time, critical where the comparator may comprise a counterfactual scenario (i.e., an alternative scenario where the ADF was not available, e.g., prior to introduction). One advantage of prospective cohort studies of sentinel high-risk populations is that they can collect rich information on clinical characteristics, other health service use, and adverse outcomes to contextualise changes apparent with ADF introduction. Adapting existing general population cross-sectional surveys and establishing online sentinel high-risk sample surveys have also been discussed as key components of ADF post-marketing monitoring. However, concerns around

representativeness of sentinel high-risk samples have been noted given the diversity of groups at high-risk for extra-medical use (e.g., populations reporting chronic non-cancer pain; opioid dependence; illicit opioid use; injecting opioid use; see 35 for further discussion).

Choice of comparators

To answer the research question, it is ideal to have a comparator from which to identify change. Changes may be measured relative to the outcomes for: non-ADF formulations of the same opioid prior to introduction (a counterfactual scenario, as in the case of a reformulation); a generic product equivalent in dosage, strength, route of administration, intended use, effects, and safety but lacking ADF properties; or to a similar but non-ADF opioid comparator (in the case of a new formulation) following ADF introduction. Where no historical or current non-ADF equivalent exists, multiple comparators with the same active moiety and/or similar levels of utilisation and rates of extra-medical use at baseline may be appropriate (44). Consideration should be given to comparison of equianalgesic doses given variation in potency between various opioids (4, 45).

There are a range of issues to consider when selecting a comparator. People who report extra-medical use often report polysubstance use, making it difficult to attribute acute (e.g., overdose) and chronic (e.g., opioid dependence) outcomes to a single substance. Further, the comparator in secondary data can only be as specific as the smallest possible unit. For example, data sources which code according to International Classification of Disease (46) (e.g., hospital separations) record only 'pharmaceutical opioid', failing to differentiate opioid type, formulation and strength (**Table 2**). Consequently, a priori selection and justification of comparators is critical, and multiple comparators may be appropriate where measuring multiple outcomes and using various data sources (4).

Table 2 here

Duration of monitoring

The duration of monitoring may depend on the study design, data source(s), outcome(s) of interest, and time for uptake of the ADF (including substitution of the non-ADF with the ADF in dispensing where a reformulation is released). In the event of a reformulation, the FDA (4) states that the baseline 'pre' introduction and observational 'post' introduction periods should be long enough to

detect outcomes which may be rare or which have large uncertainty (due to bias or variability). Whilst the aforementioned factors (i.e., study design and time for uptake of the ADF) make it difficult to propose a uniform minimum monitoring period, the duration of the pre- and post-periods should allow sufficient time to evaluate whether extra-medical opioid use occurs with exposure to the ADF, with clear justification of the duration of the monitoring period. Yet, it is acknowledged that assessing appropriate duration of monitoring is complex, particularly with low-uptake in prescribing of ADFs and the implications of this for detecting low-frequency outcomes.

Statistical analytic plan

Both guidance documents (4, 11) highlight that the statistical analysis plan should be written before commencing data collection or before commencing analysis where using existing data (4, 45). To maximise transparency, this analytic plan should include *a priori* power and sample size analyses calculated on detecting a change in primary outcomes. It is acknowledged though that *a priori* identification of power for studies aimed at signal detection (i.e., measurement of any occurrence of an event in the population) may be challenging. Efforts to pre-specify and justify the denominator used to calculate change in each outcome across each data source will also enhance transparency. To illustrate, in the case of primary data collection it may be appropriate to pre-specify whether risk of extra-medical use will be estimated based on the total group exposed to pharmaceutical opioids or on the group reporting extra-medical use. In both instances, these groups can be defined; in the first instance, as total prescriptions, number of individuals receiving prescriptions, or number of dosage units dispensed (or another unit of total exposure); and in second instance, as number reporting using a greater dose than recommended, non-prescribed use, or tampering of the specific formulation or any opioid.

The key aim is to identify outcomes associated with, and attributable to, ADF introduction (44). This is difficult when there are contemporaneous changes in the pharmaceutical opioid market, illicit drug market, and in prescribing practices which also may have impacts on extra-medical opioid use and harms. Further, there is some debate around how to identify a 'meaningful' reduction in extra-medical use and harms, including whether there should be guidance on a minimum effect size observed. In evaluating possible causality, results could be framed using the logic of Bradford Hill as

a guide (see 47 as an example), including: strength of associations (strength of relationship between exposure and outcome), consistency of findings (reproducibility across different people, settings, and samples), temporality of exposure and outcome (exposure precedes occurrence of outcome) and biological gradient (greater or lesser exposure leading to greater incidence of the outcome – noting that in some instances the exposure-outcome relationship can be more or less complex) (48). It is important that these criteria are not treated as a ‘checklist’ for causality, and rather as a guide for considering findings within and across studies (49). Indeed, there should be some consideration of competing interventions as an explanation given deployment of other strategies to address pharmaceutical opioid extra-medical use and harms (50).

STUDY CONDUCT, GOVERNANCE AND REPORTING

The following sections overview proposals specific to the conduct, governance and reporting of post-marketing studies of ADFs (**Table 3**). We summarised published post-marketing studies of ADFs identified in a recent systematic review (5) to identify key components of conduct, governance and reporting which are recommended for observational study designs (51) (see **Table 4**). As can be seen there was variation across studies, and across the different facets of study conduct and reporting, in the extent to which six features of those were noted in the studies. We explore these features further below.

Table 3 and 4 here

Funding and Industry Involvement

All products which have been approved for an ADF label in the US must be evaluated post-market introduction, and the findings reported to the FDA (52). This regulatory requirement places the onus for establishing an evidence base regarding safety and effectiveness on the pharmaceutical company. However, there is an inherent conflict of interest where the company conducts such research themselves (53, 54). We acknowledge that regulatory processes have been put in place, in part, to address this issue. Ideally though, ADF post-marketing studies would be conducted at arms-length from commercial interests. Regardless of funding source, it is advisable that study design, conduct and reporting for ADFs should undergo independent review (as detailed below) at multiple stages throughout the study. As per standard reporting guidelines (51), the name of the funder, their

role in all aspects of study design, conduct, analysis, and reporting, and any other perceived conflicts of interests (including any other industry support received by the investigators) should be explicitly disclosed in all dissemination using standard reporting forms.

Study advisory committee

An advisory (or expert) committee is a common component of clinical trials or large-scale observational studies. An advisory committee sits separate from the project team: questioning, advising, and troubleshooting to ensure rigorous study design, conduct, and reporting under agreed upon terms of reference (55, 56). This group may form an important component of studies of pharmaceutical opioid ADFs by providing an additional level of monitoring and quality assurance; lending expertise in various study designs and data sources; and ensuring concerns and priorities at the community level are raised through consumer representation.

Ideally, the committee would represent the interests of all parties involved in the research, including the research team, independent experts, consumers, and broader community. If feasible, the committee should include members who are independent of industry and the research team, and who provide a mix of statistical, clinical, epidemiological and lay/consumer backgrounds, including individuals with training in pharmaceutical science. This committee can review the study protocol, statistical analysis plan, data monitoring plan, questionnaires and other data collection tools prior to commencement; amendments to the aforementioned throughout the project; and the dissemination and publication plan at the conclusion of data collection.

Protocol publication

Increasingly, peer-review journals are now requesting submission of a prospectively published protocol or, at a minimum, a prospective statistical plan, for observational studies (57, 58). A study protocol prospectively details the data sources, populations of interest, study outcomes, choice of denominators, choice of opioid comparators, duration of monitoring, and statistical analytic plan (including power analyses). Although protocols for post-marketing studies of opioid ADFs may need to be submitted to regulatory bodies (4), ideally they should also be published in a public registry and/or in a legitimate independent peer-reviewed academic journal prior to study commencement

(59). Published study protocols improve ethical conduct, minimise selective publication and selective reporting of results by comparison against the original study aims and analytic plan, and avoid unnecessary duplication of research (60). This transparency is particularly critical for research involving pharmaceutical drugs, where there is additional concern around publication bias and selective reporting. Essential to this process is inclusion of a link to the published protocol in all subsequent dissemination; justification of deviations from the protocol; and progress updates and reports of findings in any databases where the study protocol is available.

Reporting study findings

Investment in research, participant burden, and possible impacts on practice, policy, and future research underlie an ethical obligation to publish study findings (60). This requires dissemination of research findings to the broader community, and not just to regulatory bodies as per ADF reporting requirements. However, reviews of pharmaceutical research have indicated that a substantial number of post-marketing studies are never published or, where results are not positive, published at a delay or with selective reporting of findings (61). Findings should ideally be communicated to the research community via a legitimate independent peer-reviewed (and where possible, open access) academic journal (authored according to standard criteria for authorship; 51, 62), and by making study reports submitted to regulatory bodies publicly accessible.

RECOMMENDATIONS

We outline a series of proposals for ADF post-marketing research. We advocate that all parties should be working towards more detailed guidelines on both the conduct and reporting of ADF post-marketing studies, building on existing guidance documents (4, 45), public workshops and forums on opioid ADFs (35), and the proposals raised in this paper. These reporting guidelines could include a checklist that studies are reported against, including justification of choice of study design, data source, population, comparator, duration of monitoring, analytic plan, and weighting of causal evidence within all dissemination related to the study. Guidelines can only improve research quality and enhance transparency. Thus, we believe that this recommendation can only serve to strengthen this field of research.

CONCLUSIONS

ADFs are a relatively new strategy in the response to increasing pharmaceutical opioid extra-medical use and harms. The best approaches for monitoring effectiveness have not been clearly delineated and are subject to considerable debate. Yet, the importance of progressing guidance for this field is essential given: increasing pharmaceutical opioid extra-medical use and harms; greater push to employ ADFs as a strategic response (10); insufficient evidence to conclude a net health benefit or harm from ADFs (5); and, of concern, preliminary economic modelling suggesting that healthcare costs associated with ADFs may actually be higher than non-ADF products (5). Monitoring of ADFs is complex and challenging, particularly when attempting to detect low-frequency events. The proposals outlined here might not be feasible in all research contexts and without appropriate resourcing, and other approaches not outlined here could also be borrowed from traditional and contemporary post-marketing surveillance approaches. Yet, we believe that this manuscript outlines useful recommendations in striving for best practice in study methods, conduct, design and governance. This work also reinforces the necessity for more detailed guidelines for ADF post-marketing studies, to enhance study quality, transparency, and confidence in research findings.

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Figure 1. Key outcomes

Exposure

- Any use (i.e., regardless of route/prescribing)
- Prescribed use via routes of administration as intended

Market features

- Street price
- Illicit availability

Extra-medical use (i.e., use outside the bounds of a medical professional's advice)

- Use a greater dosage than recommended by prescriber
- Use non-prescribed pharmaceutical opioid
- Tampering (crushing, dissolving, preparing for injection, etc)
- Attractiveness (ease of tampering, ease of injecting, drug liking, etc)
- Use via non-intended routes of administration (chew, snort, smoke, inject)

Associated Harms

- Extra-medical use of other pharmaceutical opioids
- Used illicit drugs
- Dependent use ('addiction')
- Non-fatal overdose
- Other acute harms (e.g., injection-related injuries and diseases)
- Fatal overdose and other related causes of death

Table 1. Example Study Designs, Data Types, Populations, and their Utility

Design	Secondary or primary data	General or sentinel population	Sensitivity	Capacity to identify rare events	Signal detection or risk quantification	Group-level or individual-level change	Timeliness
Time series	Primary	General	Low	Low	Risk quantification	No	Moderate
		Sentinel high-risk	High	Moderate			
	Secondary	General	Low	Low	Signal detection		High
		Sentinel high-risk	High	Moderate			
Cross-sectional	Primary	General	Low	Low	Risk quantification		Moderate
		Sentinel high-risk	High				
	Secondary	General	Low	Low	Signal detection		High
		Sentinel high-risk	High	Moderate			
Cohort	Primary	General	Low	Low	Risk quantification	Yes	Moderate
		Sentinel high-risk	High	Moderate			
	Secondary	General	Low	Low			High
		Sentinel high-risk	High	Moderate			

Note. **Signal detection or risk quantification:** the former is defined as measurement of any occurrence of the event, whereas risk quantification is defined as measurement of the rate of the event amongst the total sample who were at risk of the event. **Capacity to identify rare events:** is determined based on

whether it targets high risk groups for the event, sample size (statistical power) to identify events, and the variable level of detail in secondary data sources to capture data related to these events. **Sensitivity:** ability to detect change in events. **Timeliness:** ability to access data regularly to quickly detect change in events. This table lists several example study designs; other study designs (e.g., self-controlled designs) not listed here could also be considered for post-marketing studies of ADFs.

Table 2. Proposed Capacity to Measure Core Outcomes for ADF Post-Marketing Studies using Secondary Data Sources

	Exposure		Market Features		Extra-Medical Use					Harms					
	Any use	Prescribed use via intended route	Illicit availability	Street price	Use more than recommended by prescriber	Non-prescribed (diverted use)	Tampering	Attractiveness for tampering	Use via routes other than intended	Extra-medical use of other pharmaceutical opioids	Illicit drug use	Dependent use and help-seeking	Non-fatal overdose	Other acute harms (e.g., injection-related injuries and diseases)	Fatal overdose and other mortality related to opioids
Manufacturer and sales data															
Medical and prescription claims and dispensing data															
Prescription drug monitoring program data															
Ambulance data															
Emergency department data															
Hospital centre data															
Poison information/control centre data															
Adverse event reporting data															
Needle-syringe program data															
Law enforcement seizure data															
Law enforcement arrest data															
Drug treatment data															
Drug and alcohol treatment helpline call data															
Mortality data (incl. coronial investigations)															
Web-based drug market and related sites monitoring															

KEY TO PATTERNS

Measures outcome related to any pharmaceutical opioid
Measures outcome related to specific opioid type (e.g., morphine)
Measures outcome related to specific opioid type plus specific formulation (including strength, e.g., 80mg ADF product)

Table 3. Proposals for Study Conduct, Governance, and Reporting of Post-Marketing Studies of Pharmaceutical Opioid ADFs	
Funding, role of funders, and conflicts of interest	<ul style="list-style-type: none"> • Funded by industry but the design, conduct and reporting should occur independent of industry where feasible (e.g., untied educational grant) • All dissemination related to the study should explicitly declare funding, and the role of funders • All dissemination related to the study should explicitly declare any conflicts of interest, including any other sponsorship or support from industry
Advisory committee	<ul style="list-style-type: none"> • Establish an advisory committee including membership that is independent of the research team and funders who advise on study design, conduct and reporting • Ensure representation from researchers, clinicians, and consumers • Meet prior to data collection to overview study protocol and data collection materials, and analytic plan. • Meet subsequent to data collection (with other meetings as needed) to discuss protocol variations, publication plan, and dissemination of findings
Protocol	<ul style="list-style-type: none"> • Include full details and justification of each element of study design • Include power analyses to confirm sufficient statistical power to detect changes in primary outcomes prior to data collection where relevant • Ensure the protocol undergoes independent peer-review • Publish the protocol prospectively (open-access where possible) in an independent public registry and/or in a journal article where it undergoes peer-review • Link to protocol in all subsequent dissemination
Access to study results	<ul style="list-style-type: none"> • Ensure findings are reported and in an open-access or in a publicly-accessible format where undergo peer-review • Report findings according to relevant guidelines (e.g., STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement (51), Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement (62)) • Adopt standard definitions of authorship (e.g., International Committee of Medical Journal Editors authorship guidelines)

	<p>(63))</p> <ul style="list-style-type: none">• Disclose individual investigator contributions to study design, conduct and reporting
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Table 4. Review of Reporting of ADF Post-Marketing Studies Identified in a Recent Systematic Review

Study	Publication Year	Funded by industry	Declares role of funding source ¹	Declares author conflicts of interest	Declares protocol publication or published priori analysis plan	Declares a priori study registration	Published findings open-access
Butler, et al. (13)	2013	Yes	Partly (reporting only)	Yes	Not specified	Not specified	No
Cassidy, et al. (14)	2014	Not specified	Not specified	Yes	Not specified	Not specified	No
Chilcoat, et al. (15)	2016	Yes	Partly (reporting only)	Yes	Not specified	Not specified	Yes
Cicero , et al. (18)	2012	No	Yes	Yes	Not specified	Not specified	Yes
Cicero and Ellis (16)	2015	Yes	Yes	Yes	Not specified	Not specified	Yes
Cicero, et al. (17)	2016	Yes (indirectly)	Not specified	Yes	Not specified	Not specified	No
Coplan, et al. (19)	2013	Yes	Not specified	Yes	Not specified	Not specified	Yes
Coplan, et al. (64)	2016	Yes	Not specified	Yes	Not specified	Not specified	Yes
Degenhardt, et al. (20)	2015	Yes	Yes	Yes	Yes	Not specified	No
Havens, et al. (21)	2014	Yes	Yes	Yes	Not specified	Not specified	No
Hwang, et al. (22)	2015	No	Yes	Yes	Not specified	Not specified	No
Jones, et al. (23)	2016	Not specified	Not specified	Yes	Not specified	Not specified	No
Larochelle, et al. (24)	2015	No	Yes	Yes	Not specified	Not specified	Yes
Larance, et al. (38)*	2018	Yes	Yes	Yes	Yes	Not specified	No
Michna, et al. (25)	2014	Yes	Not specified	Yes	Not specified	Not specified	Yes
Peacock, et al. (26)	2015	Yes	Yes	Yes	Yes	Not specified	No
Rossiter, et al. (27)	2014	Yes	Not specified	Yes	Not specified	Not specified	Yes
Sankey, et al. (28)	2016	Not specified	Not specified	Not specified	Not specified	Not specified	No
Schaffer, et al. (39)	2018	No	Yes	Yes	Not specified	Not specified	Yes

Sessler, et al. (29)	2014	Yes	Not specified	Not specified	Not specified	Not specified	Yes
Severtson, et al. (30)	2013	Yes (indirectly)	Not specified	Yes	Not specified	Not specified	No
Severtson, et al. (31)	2016	Yes (indirectly)	Yes	Yes	Not specified	Not specified	Yes

Note. We wish to acknowledge the work of the authors of a recently published systematic review who identified the studies listed here (5); papers notated with a * were published subsequent to the review and identified by the current authorship team. Poster abstracts were not included in the current analysis.

¹The authors must declare at a minimum the role the funding source played in study design, conduct, and reporting. STROBE: STrengthening the Reporting of OBservational Studies in Epidemiology guidelines (51).

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