



**HAL**  
open science

# Adjusted trajectory of medication exposure taking into account the periodicity of dispensations and the number of dispensed packs and comparative analysis on EFEMERIS database

Cécile Chouquet, Anna-Belle Beau, Christine Damase-Michel, David Jeauneau, Isabelle Lacroix, Sabine Mercier

## ► To cite this version:

Cécile Chouquet, Anna-Belle Beau, Christine Damase-Michel, David Jeauneau, Isabelle Lacroix, et al.. Adjusted trajectory of medication exposure taking into account the periodicity of dispensations and the number of dispensed packs and comparative analysis on EFEMERIS database. 2024. hal-04735077v1

**HAL Id: hal-04735077**

**<https://hal.science/hal-04735077v1>**

Preprint submitted on 14 Oct 2024 (v1), last revised 7 Jan 2025 (v2)

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Copyright


# Adjusted trajectory of medication exposure taking into account the periodicity of dispensations and the number of dispensed packs and comparative analysis on EFEMERIS database


Cécile Chouquet<sup>1</sup><sup>\*</sup>, Anna-Belle Beau<sup>3</sup><sup>‡</sup>, Christine Damase-Michel<sup>3</sup><sup>‡</sup>, David Jeuneau<sup>1</sup><sup>□</sup>, Isabelle Lacroix<sup>3</sup><sup>‡</sup>, Sabine Mercier<sup>2</sup><sup>⊗</sup>


**1** Institut de Mathématiques de Toulouse, CNRS UMR 5219, Université Paul Sabatier Toulouse III, Toulouse, France.

**2** Institut de Mathématiques de Toulouse, CNRS UMR 5219, Université Jean Jaurès Toulouse II, Toulouse, France.

**3** Pharmacologie Médicale et Clinique, UMR INSERM 1295, Centre Hospitalier Universitaire, Faculté de médecine, Université Toulouse III, Toulouse, France.

 These authors contributed equally to this work.

 These authors also contributed equally to this work.

 Master internship

\* [cecile.chouquet@math.univ-toulouse.fr](mailto:cecile.chouquet@math.univ-toulouse.fr)

## Abstract

We presented an adjustment method for the calculation of medication exposure trajectories based on the number of dispensed packs and the type of dispensations (occasional or regular). A comparative study based on the EFEMERIS data was carried out using three different scenarios of trajectory calculation depending on whether or not the number of packs and the periodicity of medication dispensations were taken into account. The impact of the scenario was highlighted using global indicators on the number of Define-Daily Dose on all women exposed; the study of changes in individual trajectories from one scenario to another was carried out; we also compared the results of a clustering into four groups. If 65% of the trajectories remained unchanged, we could observe on the rest significant changes in number of DDD and/or on individual exposure profile. We observed 4% of trajectories that were attributed to a different cluster, and the clustering was of better quality with the adjustment method. Depending on the study context, an impact on cluster distribution could be observed for some maternal characteristics and neonatal outcomes. This was the case for a higher occurrence of neonatal pathology for neonates from mothers belonging to the cluster with high doses of psychotropics, thus reinforcing the conclusions of previous studies of a link between high exposure to psychotropic medications and presence of pathology for the newborn.

## Introduction

The challenge in measuring medication exposure lies in the different types of information available in health databases like dispensed medications, dispensing dates, number of dispensed packs, number of units per pack. A minimalist approach, and widely used so far, is to transform this information into exposed/non-exposed (possibly over time) [1, 2]. This binary approach does not consider important aspects such as

dosage, treatment duration, and timing of exposure, and leads to the quantitative and temporal aspect of the medication load being missing. In a previous study [3], a new pharmacoepidemiological method has been developed to take into account intensity and evolution of medication exposure and to estimate medication load in the form of an exposure trajectory over time. This method proposed in [3] has been applied to pregnant women exposed to psychotropic medications from the EFEMERIS database, a cohort of pregnant women and their outcomes in South-West France [4, 5]. We proposed to expand this method using another mode of calculating the medication load, which takes into account both the periodicity of medication dispensations and the number of dispensed packs.

We first recall the initial method and then describe the one developed. To assess the numerical contribution of the new calculation method versus the initial method, a comparative analysis was performed based on three scenarios, depending on whether or not the periodicity and the number of dispensed packs were taken into account. The main changes due to the proposed method on the medication exposure distribution and on exposure clusters are detailed in Section Results.

## Materials and methods

### Initial method of calculating exposure trajectories

To quantify exposure to all dispensed medications, physical quantities of medications in number of units were transformed into a standard unit of measurement proposed by the World Health Organisation: the Defined-Daily Dose, denoted by DDD [6]. Women taking psychotropic medications are often exposed to several ones (for example, antidepressant and anxiolytics) and the use of DDDs allows to aggregate units of different medications (in our case, the different types of psychotropic medications). Exposure periods were computed from dispensation dates and number of units per pack. The number of dispensed packs was not available and set at 1 by default. In a general manner, it is assumed that for each dispensed medication, women are exposed to one DDD per day (cf. [3]). For example, for one dispensed pack of 7 DDD, the treatment duration was estimated at 7 days with one DDD per day. If 14 DDDs were dispensed, the treatment duration was estimated at 14 days. Thus, in the initial mode of calculation, the treatment periods of the same active substance were placed one after the other. In case of pregnancy, some DDDs could be shifted after birth and were therefore not taken into account in the calculation of the exposure measurement. This computation could be applied to a medication, or several medication of the same class: after superimposing individual periods of exposure, the number of DDDs per day and per medication was cumulated for all psychotropic medications dispensed on a given day of a woman's pregnancy. A sequence of daily quantitative measurements of psychotropic exposure was therefore available for each woman, which could be called daily exposure trajectory.

### Proposed method of calculating exposure trajectories based on periodicity adjustment

In case where the number of dispensed packs was available, the first step was to calculate the total number of units dispensed at each dispensation of a specific medication (identified using the ATC code) in order to estimate the active medication load closer to reality. Then, the periodicity was included by differentiating single or occasional dispensing from regular dispensing. A dispensation was considered as single or occasional if it was not renewed over a period of 45 days. In this case, the

distribution of the corresponding total DDDs was done as for to the initial method, ie. put one after the other with one DDD per day. Dispensations were defined as regular if they were repeated in a period of less than 45 days, based on French dispensing habits for one month of treatment, adding a flexibility of 15 days. If a specific medication was dispensed regularly for a woman, we calculated the average number of DDDs dispensed over all regular dispensations ( $\bar{N}_{DDD}$ ) and the average duration between two regular dispensations ( $\bar{D}_{between}$ ). We deduced the ratio  $F = \bar{N}_{DDD}/\bar{D}_{between}$  which estimated, for the considered pregnancy, the number of DDDs per day distributed between the first and the last regular dispensation. From the last dispensation, the remaining number of DDDs per day was  $F/2$  until exhausted to consider possible weaning.

As the initial method, we then deduced the total number of DDDs per day by cumulating all medications of interest (psychotropic) dispensed on a given day of a woman's pregnancy. In this study, we also cumulated the exposure measurement by week, to obtain weekly exposure trajectory for each exposed pregnancy.

## Data

Data for our analysis comes from the EFEMERIS database [4,5]. The EFEMERIS cohort was approved by the French Data Protection Authority on 7 April 2005 (authorization number 05-1140). This study was performed on anonymized patient data. The women included in the EFEMERIS database were informed of their inclusion and of the potential use of their anonymized data for research purposes. They could oppose the use of their data at any time. The women included in the EFEMERIS database know that their collected and anonymized data can be used for medical research purposes and can thus be published. The study was approved by the EFEMERIS steering group. Data were handled and stored in accordance with the General Data Protection Regulation. The EFEMERIS database contains data about medication dispensed to pregnant women (from CPAM, the national medical insurance organisation) in Haute-Garonne, data concerning pregnancy outcomes and data on the children obtained from mother-and-child health services (PMI, "Protection Maternelle et Infantile", which records information about the child and delivers the mandatory health certificates for children at eight days, nine months and 24 months of age). We also have information on pregnant women such as age, presence of diabetes or preeclampsia. The present study was restricted to mother-child pairs included in EFEMERIS between June 1, 2011 and December 31, 2020. Over this period, we retrieved 24,138 psychotropic medication dispensations among 6,820 live pregnancy outcomes for which the presence or absence of neonatal pathology was known. The statistical unit of our study was the pair, pregnancy-outcome of pregnancy, which will be noted pregnant woman or pregnancy in the following document in the absence of ambiguity. In this context, for each pregnancy, the exposure trajectory described the exposure to psychotropic medications. More precisely, the exposure trajectories started from 4 weeks before pregnancy to take into account the potential long-term presence of medications in the woman's body and its potential effect on the fetus from the start of pregnancy. To calculate such an exposure trajectory from 4 weeks before pregnancy, medication dispensations from week -13 were used, because a treatment taken at -4 have been dispensed between -13 and -4. But DDD before -4 were not considered for analysis of exposure trajectories. Weekly measures of exposure to psychotropic medications were calculated for each pregnant woman exposed at least once between -4 weeks before pregnancy and the end of pregnancy, called pregnancy period in the rest of this document.

## Comparative analysis approach

We considered the three following scenarios for our comparative study to assess the contribution of the proposed method:

- Scenario 1: As if the number of dispensed units were not available (set by default at 1) and no periodicity adjustment,
- Scenario 2: Available number of dispensed units and no periodicity adjustment,
- Scenario 3: Available number of dispensed units and periodicity adjustment.

For each scenario, we computed some global indicators on the whole set of the trajectories of exposed pregnancies, gathered in Table 1. We first assessed the change of number of exposed pregnancies due to the number of packs dispensed during week -13 and -5 and the periodicity adjustment. The sum of DDDs during the pregnancy period was calculated to evaluate the change of the DDD number between scenarios. As the number of exposed pregnancies changed between scenarios, we also computed the average DDD per week, the standard deviation, the 90 and 95 percentile, and the maximum. In a second step, the individual trajectories for each pregnancy were computed and compared using the three scenarios. The percentage of pregnancies without any change of trajectories between scenarios was calculated. When a change occurred, the variation from one scenario to another of the total of DDDs was quantified and these values were analysed. In a last step, we evaluated the impact of the scenario on the creation of exposure clusters. As in [3], we used the Kmeans method for longitudinal data, an unsupervised clustering method based on an algorithm for which the aim is to partition the observations (here the trajectories) into a given number of clusters. In this last step, we examined distribution by cluster of some maternal characteristics and neonatal outcomes such as neonatal pathology.

## Results and discussion

In our study population, we observed that 28% of the psychotropic exposed pregnancies had more than one pack of psychotropic medication dispensed at least once. By reasoning on the number of dispensing, this concerned 32% of all the dispensing.

### Step 1: Comparison on DDD values distribution (Table 1)

Remember that the trajectories were calculated from dispensing from 13 weeks before pregnancy. This could impact whether a pregnancy was classified as exposed from 4 weeks before pregnancy and thus could change the exposure trajectory. Taking into account the number of dispensed units (from scenario 1 to 2) allowed to recover 94 pregnancies, and adding the periodicity adjustment (from scenario 2 to 3) allowed to recover 29 more pregnancies, ie. an increase of 2.4% in the number of pregnancies exposed at least one week between -4 and 38 weeks of pregnancy (second column of Table 1). The sum of DDDs increased by 32% from scenario 1 to 2 and by 42% from scenario 1 to 3 across global trajectories of all exposed pregnancies (third column of Table 1). Considering only the impact of the periodicity adjustment (from scenario 2 to 3), the total DDDs increased globally by 7%.

Note that the increase in the sum of DDD between scenarios 1 and 2 was due to the fact that there were more pregnancies classified as exposed and that exposure measures were logically increased if the number of units is greater than 1. The increase from scenario 2 to 3 was also explained by the fact that in scenario 2, some DDDs were shifted after the end of pregnancy, while with scenario 3, the periodicity adjustment

allowed them to be positioned more appropriately during pregnancy period. The average number of weekly DDD by pregnancy increased for example from 47.3 for scenario 1 to 65.6 for scenario 3, ie. almost 20 DDD more over the entire pregnancy period (from -4 to around 38 weeks). We also studied the weekly DDD distribution (four last columns of Table 1). The periodicity adjustment had the effect of largely increasing the maximum DDDs as well as the largest values (see the 95 percentiles). But the average increased slightly, due the fact that at least 75% of the DDDs were equal to 0 for each of the three scenarios.

**Table 1. Indicators of comparison of DDD values between the three scenarios**

	Number of exposed pregnancies at least one week between -4 and 38	Sum of DDDs between -4 and 38	Distribution of weekly DDD			
			Mean (sd)	90 percentile	95 percentile	max
Scenario 1	5468	258427	1.13 (3.00)	6.5	7.0	47
Scenario 2	5562	341656	1.47 (3.60)	7.0	7.0	50
Scenario 3	5591	366485	1.57 (4.06)	6.5	8.7	84

## Step 2: Impact on individual trajectories

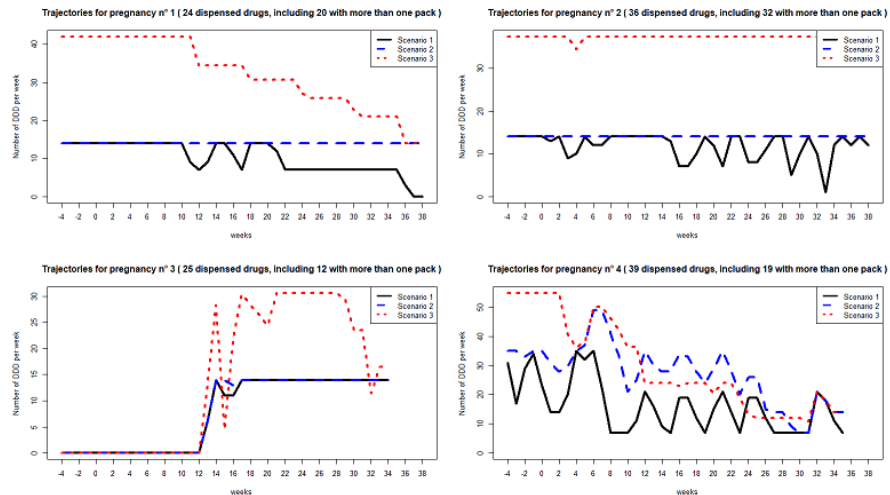
Step 2 considered the pairwise differences between the three trajectories of each exposed pregnancy. From scenario 1 to 2 (adding the number of dispensed units), 68% of pregnancies had a different trajectory, ie. at least one week with a different DDD, which was consistent with the percentage of dispenses of only one pack. Only 10% of trajectories increased on average by at least one DDD per week, and up to 10 DDD per week.

From scenario 2 to 3 (adding the periodicity adjustment), 65% of the trajectories were strictly identical. Among the 35% of pregnancies having different trajectories, one third had a total of DDDs decreased with a maximum drop corresponding to an average of 3 DDDs per week. This decrease could be explained mainly by the modified calculation of DDD before -4 weeks which could lead to a greater number of DDDs before week -4 and therefore lower after. Half of the modified trajectories realized an increase of the total DDDs corresponding to 1.3 DDDs per week on average with standard deviation equal to 2.1. For the rest of these modified trajectories, the total of DDDs did not change due to a compensation effect between weeks. We observed 2% of all trajectories (ie. 106 trajectories) associated with an augmentation of the total of DDD of between approximately 2 and 20 DDD per week on average.

Fig 1 represents examples of trajectories calculated according to the 3 scenarios for 4 exposed pregnancies. For these four pregnancies, the number of dispensations was between 24 and 39 corresponding to between 2 and 7 different dispensed ATC, with half of dispensations of more than one pack. In the three first examples, we observed that taking into account the number of packs was mainly enhanced by the periodicity adjustment. This revealed changes in the trajectory profiles: a higher exposure at the start of pregnancy, followed by a gradual decrease for pregnancy n°1, a higher exposure throughout the pregnancy period for pregnancy n°2 and a medication load multiplied by 2 after the first trimester of pregnancy for pregnancy n°3. The changes were less significant for the pregnancy n°4.

## Step 3: Impact on clustering

Using the individual weekly exposure trajectories calculated with scenario 2 and 3, we used the Kmeans method for longitudinal data to create exposure clusters. We



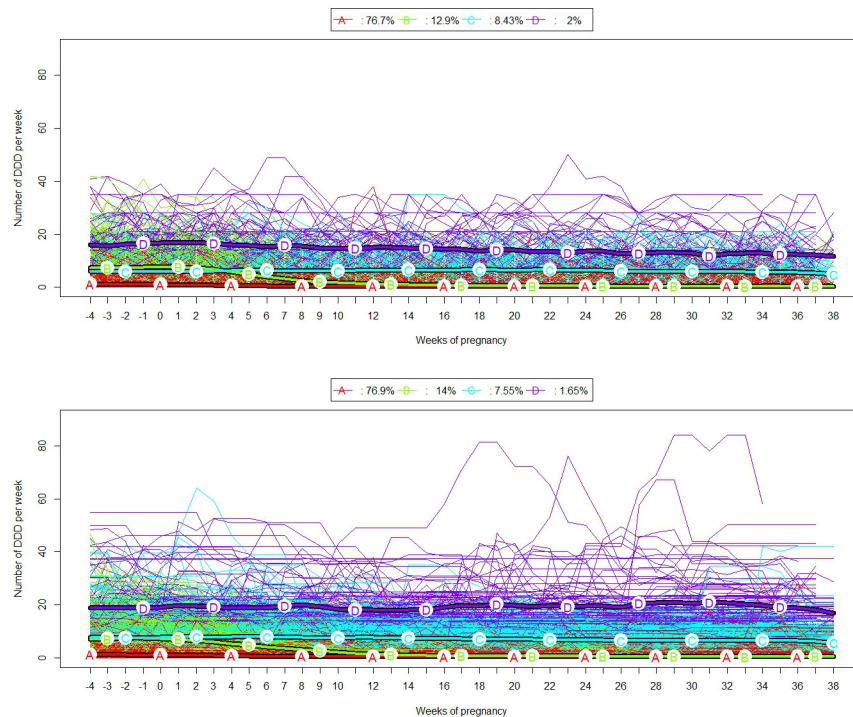
**Fig 1. Examples of individual exposure trajectories.** Examples of exposure trajectories calculated according to three calculation scenarios, for four exposed pregnancies. The woman of pregnancy n°1 received 24 medication dispensations of 3 different ATC over the pregnancy period, of which 20 with more than one pack. The woman of pregnancy n°2 received 36 medication dispensations of 2 different ATC over the pregnancy period, of which 32 with more than one pack. The woman of pregnancy n°3 received 25 medication dispensations of 2 different ATC over the pregnancy period, of which 13 with more than one pack. The woman of pregnancy n°4 received 39 medication dispensations of 7 different ATC over the pregnancy period, of which 19 with more than one pack.

evaluated the impact of using the periodicity adjustment on the creation of exposure clusters by comparing the clustering from scenario 2 and 3. The quality of the clustering measured by the Calinski-Harabatz criterion was better for scenario 3: 2302 for scenario 3 versus 2010 for scenario 2. Based on four clusters (see [3]), it could be seen that taking into account the periodicity adjustment did not change the representative trajectory profile of the four clusters (see Fig 2). The average level of exposure by cluster remained stable, except for the cluster corresponding to the highest exposures: on average, over individual trajectories, 706 DDD (standard deviation=291) for scenario 2 versus 800 (sd=267) for scenario 3). The study of the concordance between the two partitions showed that 4% of trajectories of exposed pregnancies changed clusters between the two scenarios.

We studied the impact of these 4% of trajectories on the cluster distribution of some maternal characteristics (such as pre-eclampsia and diabetes) and neonatal outcomes (such as neonatal pathologies or preterm birth) not taken into account in the formation of the clusters. Concerning variables affecting the mother, it was observed for example that the proportion of pre-eclampsia per cluster remains unchanged from one scenario to another, but there is a higher proportion of diabetes reported among pregnancies in the high-exposure cluster in scenario 2 (19.5%) as compared with scenario 1 (15%). For variables concerning the newborn, the proportion of premature births remained unchanged from one scenario to another. But it was observed that the proportion of neonatal pathology in high-exposure clusters increased with the periodicity adjustment from 21.6% (out of 111 pregnancies) to 26% (out of 92 pregnancies).

These elements suggested that depending on the study conducted and the choice of considered variables, taking into account the periodicity adjustment does not change the conclusions of the study, but can refine them. In the case of the presence of neonatal

pathology, it reinforced the results of the study conducted in [7] on the link between exposure to psychotropic medications and the presence of neonatal pathology. On this example with the EFEMERIS database, taking into account or not of the periodicity adjustment did not radically modify the results, but the quality of the clustering is better and the trend of the main results is strengthened.



**Fig 2. Individual exposure trajectories and mean trajectories for clusters.** Four clusters were identified by K-means method for longitudinal data. Individual trajectories in the same cluster are plotted in the same color. The top figure represents the exposure trajectories calculated according to scenario 2, and the bottom one according to scenario 3.

## Conclusion

In the case where the number of dispensed packs was available, we highlighted an impact of adjusting the calculation of exposure measure by taking into account the periodicity of dispensations. The analyzes on the total number of DDDs over all trajectories or on individual ones showed that the method increased the average exposure measure quite slightly. 65% of the exposed pregnancies did not have any change in the weekly trajectories using the different methods. Among the changed trajectories, 90% showed an increase or a decrease of the cumulative medication exposure, and the remaining 10% had changes according to the weeks that are compensated. There could be a great variability in changes in the medication exposure and thus for a non-negligible number of trajectories, an increased number of DDDs and a modified exposure trajectory profile could be observed. The adjusted trajectories led to clusters with no radical modifications but with better quality and higher level of exposure for the women most exposed. Considering others variables, adjustment variables or outcomes in pharmacoepidemiology studies, their distribution by cluster could be impacted or not.



## Acknowledgments

230

We thank Caroline Hurault-Delarue who provided the foundation for the work in her Phd, and Anthony Caillet for the data extraction.

231

232

## References

1. Grzeskowiak LE, Gilbert AL, Morrison JL. Exposed or not exposed? Exploring exposure classification in studies using administrative data to investigate outcomes following medication use during pregnancy. *Eur J Clin Pharmacol*. 2012;68(5):459–467. 3.
2. Pazzagli L, Linder M, Zhang M, et al. Methods for time-varying exposure related problems in pharmacoepidemiology: an overview. *Pharmacoepidemiol Drug Saf*. 2018;27(2):148–160.
3. Hurault-Delarue C, Chouquet C, Savy N, Lacroix I, Beau AB, Montastruc JL, Damase-Michel C. How to take into account exposure to drugs over time in pharmacoepidemiology studies of pregnant women? *Pharmacoepidemiol Drug Saf*. 2016 Jul;25(7):770-7. doi: 10.1002/pds.4000. Epub 2016 Mar 27. PMID: 27018245.
4. Lacroix I, Hurault C, Sarramon MF, Guitard C, Berrebi A, Grau M, Albouy-Cossard C, Bourrel R, Elefant E, Montastruc JL, Damase-Michel C. Prescription of drugs during pregnancy: a study using EFEMERIS, the new French database. *Eur J Clin Pharmacol*. 2009 Aug;65(8):839-46.
5. Hurault-Delarue C, Lacroix I, Vidal S, Montastruc JL, Damase-Michel C. Médicaments et grossesse: étude dans la base de données EFEMERIS 2004-2008 [Drugs in pregnancy: study in the EFEMERIS database (2004 to 2008)]. *Gynecol Obstet Fertil*. 2011 Oct;39(10):554-8. French. doi: 10.1016/j.gyobfe.2011.07.044. Epub 2011 Sep 15. PMID: 21924656.
6. Wood ME, Lupattelli A, Palmsten K, Bandoli G, Hurault-Delarue C, Damase-Michel C, Chambers CD, Nordeng HME, van Gelder MMHJ. Longitudinal Methods for Modeling Exposures in Pharmacoepidemiologic Studies in Pregnancy. *Epidemiol Rev*. 2022 Jan 14;43(1):130-146. doi: 10.1093/epirev/mxab002. PMID: 34100086; PMCID: PMC8763114.
7. Hurault-Delarue C, Chouquet C, Savy N, Lacroix I, Beau AB, Montastruc JL, Damase-Michel C. Interest of the trajectory method for the evaluation of outcomes after in utero drug exposure: example of anxiolytics and hypnotics. *Pharmacoepidemiology and Drug Safety* 2017 May; 26(5):561-569. doi.org/10.1002/pds.4199