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| Requirement Documentation  MYELOFIBROSIS (MF) Longitudinal Patient Data Analysis |
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|  |
| Author: Mohit Thukral, Anuj Kumar  Date: Feb 08, 2016  Version: 1.0 |

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# Signature page

**Program(s) covered by this document**

|  |  |
| --- | --- |
| **Program** | **Version** |
| 13177\_MF\_Intial\_Data\_understanding\_autorecovery\_2016\_01\_19 |  |
| 1. Libname |  |
| 2. Import Data |  |
| 3. Index date and lookback analysis |  |
| 3.1 Index Date and LB |  |
| 4. Primary cancer |  |
| 4.1 Primary cancer |  |
| 5. Demographic |  |
| 6. Regimen Analysis |  |

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Programmer Date

# Introduction

Program documentation must be written together with the code. The objective of this technical document is to facilitate ease of maintenance and to detail code logic and parameterisation.

# Reference documents (To be updated)

|  |  |
| --- | --- |
| **Document** | **Location or N/A** |
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# Description

## Purpose of the Document

This document gives the information about the assumptions and definitions of variable and logic used in the study.

## Input dataset(s)

**Datasets used in analysis:**

VISIT

DIAGNOSIS

DRUG\_R

INPATIENT

LAB\_R

LABS

MEASUREMENT

MEDADMIN

MEDCLAIMS

OBSERVE

PRO

PROCEDURE

RXCLAIMS

RXWRITTEN

PATIENT

**Other datasets not used in analysis:**

BIOMARKER

CARE

ENCOUNTER

INSURANCE

MEMBERDET

# Change log

*The version changes correspond to the upgrade of the program code.*

| **Ver: #** | **Date** | **Reason for change** | **Init.** |
| --- | --- | --- | --- |
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# Definitions of key terms:

## First active date: Earliest date of any treatment recorded in the database

Following “Dataset” and “Variable” were considered for first active date calculation:

|  |  |
| --- | --- |
| **Dataset** | **Variable** |
| DIAGNOSIS | DIAG\_DATE |
| DRUG\_R | NOTE\_DATE |
| INPATIENT | ADMIT\_DATE |
| LAB\_R | FST\_DT |
| MEDADMIN | ORDER\_DATE |
| MEDCLAIMS | FST\_DT |
| OBSERVE | OBS\_DATE |
| PRM | REPORTED\_DATE |
| PROCEDURE | PROC\_DATE |
| RX | RXDATE |
| RXCLAIMS | FILL\_DT |
| VISIT | VISIT\_START\_DATE |

## Index date: Earliest date of any treatment/diagnosis recorded in the database specific to PMF/SMF defined by ICD 9 code of interests (PMF: 238.76; SMF: 289.83)

## Following Dataset and Variable were considered for index date calculation

|  |  |
| --- | --- |
| **Dataset** | **Variable** |
| INPATIENT | PTID, ADMIT\_DATE, DIAG1, DIAG2, DIAG3, DIAG4, DIAG5 |
| MEDCLAIMS | PTID, FST\_DT, DIAG1, DIAG2, DIAG3, DIAG4, DIAG5 |
| DIAGNOSIS | PTID, DIAG\_DATE, DIAGNOSIS\_CD |
| RXCLAIMS | FILL\_DT |
| MEDCLAIMS | FST\_DT |
| RXWRITTEN | RXDATE |
| MEDADMIN | ORDER\_DATE |
| PRO | REPORTED\_DATE |

Treatment with Jakafi (core drug for MF) has been considered for index date identification

If a patient has no diagnosis of PMF/SMF, in that case first date of Jakafi used has been considered as index date and category is assigned as PMF. But there were no such cases. All the patients have been diagnosed with PMF and/or SMF.

PMF/SMF patient’s identification:

1. The first PMF diagnosis date and first SMF diagnosis date were identified for each patient from the DIAGNOSIS, MEDCLAIM and INPATIENT data sets.
2. Patients were initially grouped as PMF or SMF based on their associated earliest diagnosis date, and such diagnosis date has been defined as the index date.
3. Patients whose index diagnosis was PMF, with at least a 90+ day lookback period from the index date, without prior PV (238.4) or ET (238.71) diagnosis were included in the analysis under the PMF category.
4. Patients diagnosed with either PMF or SMF with prior history of PV/ET were included in the analysis under the SMF category.
5. Patients diagnosed with SMF, without prior history of PV/ET were included in the analysis under the Other SMF category.

## Age of the patient: Patient age at index date

## Following Dataset and Variable contains birth year of patient information

|  |  |
| --- | --- |
| **Dataset** | **Variable** |
| PATIENT | BIRTH\_YR |

## Lookback period: Defined maximum period before the index date in which any record is available for a patient.

## This period is calculated as:

## lookback=index\_dt - first\_act\_dt ;

## NDC codes (5-4-2): Exhaustive list of NDC codes for MF drugs from FDA website (database accessed on Oct 21, 2015), Master NDC file (with Smart analyst) and NDC code list for Multiple Myeloma (Optum Data Analysis) project

### Procedure codes: Exhaustive list of procedure codes from “Find a Code”

### website for MF drugs <https://www.findacode.com/search/search.php> and HCPCS code list received from Optum in Multiple Myeloma (Optum Data Analysis) project (filename: *NDC\_HCPCS\_from optum-2015-06-01.xlsx*)

### Padding of NDC codes: Padding is done for the NDC codes where NDC

### code length is less than 11 digits.

### If length(ndc) lt 11 and ndc not in (" " , "NONE", "UNK") then ndc=repeat('0',11-length(ndc)-1)||ndc;

Applied to following datsets:

RXWRITTEN, MEDADMIN, RXCLAIMS, PRO and MEDCLAIMS

## Drug data: Using the drug name, NDC code list and procedure code list MF drug related records are fetched from the study database and records are de-duplicated (same patient, same drug on same date).

## The dataset so formed is called drug data

|  |  |
| --- | --- |
| **Dataset** | **Variable** |
| PROCEDURE | PROC\_DATE, PROC\_CODE |
| MEDCLAIMS | FST\_DT, PROC\_CD, NDC |
| MEDADMIN | ORDER\_DATE, NDC |
| PRO | REPORTED\_DATE, NDC |
| RXCLAIMS | FILL\_DT, DAYS\_SUP, NDC |
| RXWRITTEN | RXDATE, DAYS\_SUPPLY, NDC |
| DRUG\_R | NOTE\_DATE, GENERIC\_NAME |

# BUSINESS RULES TO DEFINE LINE OF TREATMENT

**Inclusion/exclusion criteria**

* Clear look-back (no other MF diagnosis or drug usage) of minimum 90 days
* Minimum age for inclusion: 18
* Other primary cancer diagnosis prior to index date has no role in excluding/including patients

**Relevant diagnosis codes (ICD9) for MF\*:**

Primary MF: 238.76

Secondary MF: SMF (289.83), Post PV-MF (PV: 238.4) or Post ET-MF (ET: 238.71)

PV: Polycythemia vera; ET: Essential thrombocytopenia

**Line of Treatment in Myelofibrosis**

1. The usage of each core MF drug, steroid and other MF drug will be analyzed individually:
2. Treatment period for a drug would be the period from the first date of use to the last date of use. The latter is the date when there is at least a 90 day gap between the day the supply of a claim for a drug is exhausted and the day of the next claim for the same drug. See 1c for imputation rules for assigning the days of supply for a particular drug.
3. A drug used multiple times with a gap of 90 or more days will have multiple treatment periods (start dates and end dates)
4. For an oral therapy, the end date for each treatment period would be the last Rx date in that treatment period + days supply (days supply is assumed to be to be 30 days (in case the data is not present in claims data or days supply is less than 15 days) for all oral therapies while that for injectable would be the last Rx date plus estimated clinical benefit of 30 days).

(Analysis of claims data showed that in >95% of drug claims, difference between two consecutive prescriptions is less than 60 days. Therefore, period of 60 days has been considered)

1. Once the different treatment periods of each MF drug have been identified, these periods are lined up such that the entire treatment duration for a patient is broken up into multiple intervals, each with a distinct regimen (i.e. a single drug or a combination of drugs). Each such successive interval is deemed to be a different line of treatment for a patient, subject to the below stipulations:
2. If a regimen comprises of Jakafi (only drug approved to treat MF patients) and any other MF drug, the regimen will be replaced with only Jakafi.
3. If a regimen comprises an ‘other MF drug(s)’ along with a steroid, the regimen will be replaced with only the ‘other MF drug(s)’. In other words, the steroid will be deleted from the regimen. If this regimen is <30 days, disregard the regimen and replace by a blank
4. If a regimen comprises only a steroid(s), the regimen will be disregarded and replaced by a blank, if the duration of the regimen is <30 days. Else, the regimen will stand and no change or adjustment will be made
5. Upon completion of each of steps a-c and prior to proceeding to next step, all successive LOTs that are identical (regimens should be exactly the same) and occur without any gap between them will be merged into the same LOT
6. **If there is a blank regimen of <30 days:** 
   1. If preceding and succeeding regimens are the same; then the preceding regimen will be deemed to continue till the end date of the regimen succeeding the blank regimen.
   2. If the preceding and succeeding regimens are different then these would be considered as two different regimens and the blank regimen will be disregarded.

(RATIONALE FOR THE ABOVE: During treatment with any regimen, a gap of up to 30 days could exist on account of compliance or adverse events. Therefore, i) if the preceding and succeeding regimens are similar, the 2 periods would be treated as continuous; ii) In all other cases they would be treated as two different regimens)

1. **If there is a blank regimen of 30-89 days:**
2. If preceding and succeeding regimens are the same; then the preceding regimen will be deemed to continue till the end date of the regimen succeeding the blank regimen.
3. If the preceding and succeeding regimens are different then these would be considered as two different regimens and the blank regimen will be disregarded.

(RATIONALE FOR THE ABOVE: During treatment with any regimen, a gap of up to 90 days could exist on account of compliance or adverse events. Therefore, i) if preceding and succeeding regimen are similar, both would be merged, and ii) if preceding and succeeding regimen are not similar then they would be treated as two different regimens)

1. **If there is a blank regimen of >90 days:**
2. Preceding and succeeding regimens would be considered as two different regimens irrespective of both being the same or if both are different. The blank regimen will be disregarded.
3. Every LOT so formed (and comprising either Busulphan/ Melphalan/cyclophosphamide, etc) on the basis of 1 and 2 above will be checked to see if there is evidence of allogenic SCT within 15-21 days of the end of the preceding regimen. If there is,
   1. The SCT will be considered part of the same LOT as the MF related drug (which will be the conditioning regimens)

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**List of MF Drugs:**

Core drug: RUXOLITINIB

Steroids: DEXAMETHASONE, PREDNISOLONE

Other MF drugs: BUSULFAN, CYCLOPHOSPHAMIDE, DANAZOL, ERYTHROPOIETINS, FLUDARABINE, FLUOXYMESTERONE, HYDROXYUREA, LENALIDOMIDE, MELPHALAN, NANDROLONE DECANOATE, OXYMETHOLONE, POMALIDOMIDE, THALIDOMIDE, METHANDROSTENOLONE\*

\* NDC code not available on FDA website

**List of drugs to be considered for MF (As received from LS team) :-**

For hematological symptoms:

* Erythropoiesis stimulating agents (erythropoietin)
* Androgenic agents (Danazol, Nandrolone, ﬂuoxymesterone, methandrostenolone, and oxymetholone, etc.)
* ImiDs (Thalidomide/lenalidomide/pomalidomide)
* Corticosteroids (Prednisolone) – palliative care in case all the drugs fail

For Splenomegaly:

* Jakafi (Ruxolitinib)
* Hydroxyurea
* Busulphan
* Melphalan

Conditioning regimen before allo-SCT

* Myeloablative SCT: Busulphan and cyclophosphamide
* RIC: Fludarabine and busulphan

\*Reference:

We have considered Post PV-MF and Post ET-MF as SMF based on the following guidances:

         Most of the treatment practice guidelines consider MF post ET and post PV as secondary MF and these patients are essentially treated similar to PMF

(Source: 1. [Cervantes, Blood, 2014, 124 (17)](http://www.bloodjournal.org/content/124/17/2635?sso-checked=true); 2. [Jakafi Label](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202192s009lbl.pdf) for MF patients is in patients with either PMF or post PV-MF and post ET-MF).

         Most of the ongoing trials in MF include patients, who are either PMF or have progressed to MF from PV and ET.

o   Imetelstat trials: [NCT02426086](https://clinicaltrials.gov/ct2/show/NCT02426086); [NCT01731951](https://clinicaltrials.gov/ct2/show/NCT01731951?cond=myelofibrosis&intr=imetelstat&rank=1)

o   Pacritinib trials: [PAC-326](https://clinicaltrials.gov/ct2/show/NCT02055781?cond=myelofibrosis&intr=pacritinib&rank=1); [PERSIST-1/PAC325](https://clinicaltrials.gov/ct2/show/NCT01773187?cond=myelofibrosis&intr=pacritinib&rank=2)

o   Momelotinib trials: [SIMPLIFY-1](https://clinicaltrials.gov/ct2/show/NCT01969838?cond=myelofibrosis&intr=momelotinib&rank=1); [SIMPLIFY-2](https://clinicaltrials.gov/ct2/show/NCT02101268?cond=myelofibrosis&intr=momelotinib&rank=3); [NCT01423058](https://clinicaltrials.gov/show/NCT01423058) ; [NCT02515630](https://clinicaltrials.gov/show/NCT02515630) ; [NCT01236638](https://clinicaltrials.gov/show/NCT01236638)