Analysis of the interval from MA to HTA with Shiny

Victoria Zaitceva

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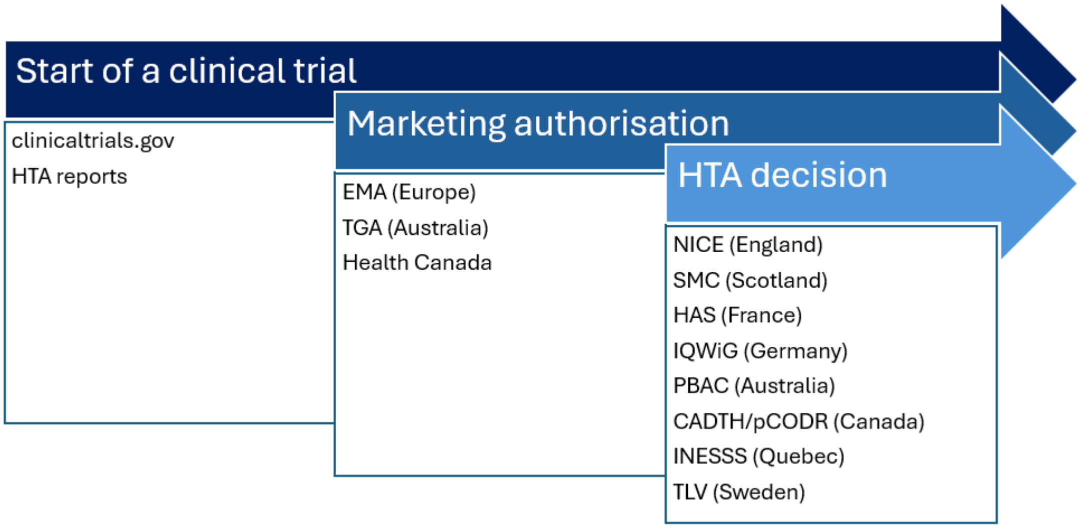
Motivation for this project:

- predictable timelines for patients
- evaluating regulatory bodies' performance and learning by international comparison
- transparency in HTA processes

Data Sources Overview



Start of a clinical trial

clinicaltrials.gov
HTA reports

Marketing authorisation

EMA (Europe)
TGA (Australia)
Health Canada

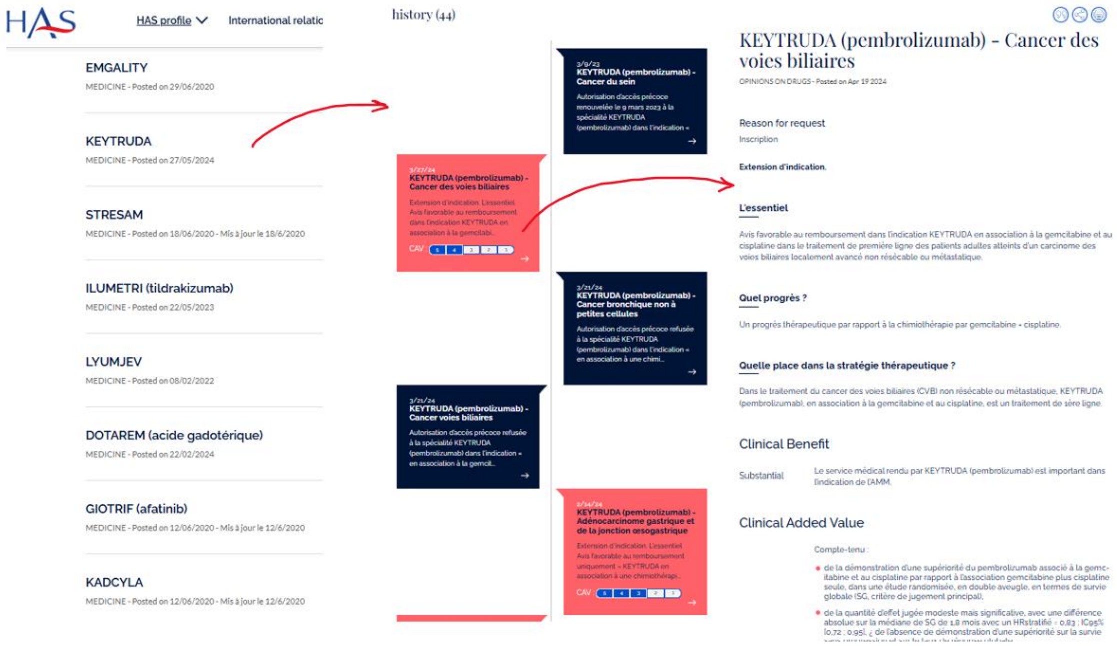
HTA decision

NICE (England)
SMC (Scotland)
HAS (France)
IQWiG (Germany)
PBAC (Australia)
CADTH/pCODR (Canada)
INESSS (Quebec)
TLV (Sweden)

Clinical trials data

```r
library(ctrialsgov)
library(DBI)
library(RPostgres)

# Initiating the PostgreSQL driver
drv <- dbDriver('PostgreSQL')

# Establish a connection to the PostgreSQL database
con <- dbConnect(drv, dbname="aact",host="aact-db.ctti-clinicaltrials.org",
                 port=5432, user="XXX", password="XXX")


all_trials <- ctgov_create_data(con)
```

HTA data - web scraping example



HAS profile

International relatic

EMGALITY
MEDICINE - Posted on 29/06/2020

KEYTRUDA
MEDICINE - Posted on 27/05/2024

STRESAM
MEDICINE - Posted on 18/06/2020 - Mis à jour le 18/6/2020

ILUMETRI (tildrakizumab)
MEDICINE - Posted on 22/05/2023

LYUMJEV
MEDICINE - Posted on 08/02/2022

DOTAREM (acide gadotérique)
MEDICINE - Posted on 22/02/2024

GIOTRIF (afatinib)
MEDICINE - Posted on 12/06/2020 - Mis à jour le 12/6/2020

KADCYLA
MEDICINE - Posted on 12/06/2020 - Mis à jour le 12/6/2020

history (44)

3/9/23
KEYTRUDA (pembrolizumab) - Cancer du sein
Autorisation d'accès précoce renouvelée le 9 mars 2023 à la spécialité KEYTRUDA (pembrolizumab) dans l'indication «

3/27/24
KEYTRUDA (pembrolizumab) - Cancer des voies biliaires
Extension d'indication. L'essentiel Avis favorable au remboursement dans l'indication KEYTRUDA en association à la gemcitabi...
CAV : 5 4 3 2 1

3/21/24
KEYTRUDA (pembrolizumab) - Cancer bronchique non à petites cellules
Autorisation d'accès précoce refusée à la spécialité KEYTRUDA (pembrolizumab) dans l'indication « en association à une chimi...

3/21/24
KEYTRUDA (pembrolizumab) - Cancer voies biliaires
Autorisation d'accès précoce refusée à la spécialité KEYTRUDA (pembrolizumab) dans l'indication « en association à la gemcit...

2/14/24
KEYTRUDA (pembrolizumab) - Adénocarcinome gastrique et de la jonction œsogastrique
Extension d'indication. L'essentiel Avis favorable au remboursement uniquement « KEYTRUDA en association à une chimiothérap...
CAV : 5 4 3 2 1

KEYTRUDA (pembrolizumab) - Cancer des voies biliaires

OPINIONS ON DRUGS - Posted on Apr 19 2024

Reason for request

Inscription

Extension d'indication.

L'essentiel

Avis favorable au remboursement dans l'indication KEYTRUDA en association à la gemcitabine et au cisplatine dans le traitement de première ligne des patients adultes atteints d'un carcinome des voies biliaires localement avancé non résécable ou métastatique.

Quel progrès ?

Un progrès thérapeutique par rapport à la chimiothérapie par gemcitabine + cisplatine.

Quelle place dans la stratégie thérapeutique ?

Dans le traitement du cancer des voies biliaires (CVB) non résécable ou métastatique, KEYTRUDA (pembrolizumab), en association à la gemcitabine et au cisplatine, est un traitement de 1ère ligne.

Clinical Benefit

Substantial	Le service médical rendu par KEYTRUDA (pembrolizumab) est important dans l'indication de l'AMM.

Clinical Added Value

Compte-tenu :

- de la démonstration d'une supériorité du pembrolizumab associé à la gemcitabine et au cisplatine par rapport à l'association gemcitabine plus cisplatine seule, dans une étude randomisée, en double aveugle, en termes de survie globale (SG, critère de jugement principal),
- de la quantité d'effet jugée modeste mais significative, avec une différence absolue sur la médiane de SG de 1,8 mois avec un HRstratifié = 0,83 ; IC95% [0,72 ; 0,95], ¿ de l'absence de démonstration d'une supériorité sur la survie

```
<li class="itResultat">
    <div class="itResultat--content">
        <div class="card-item">
            <div class="content">
                <h3 class="title"><a href="jcms/pprd_2982864/en/keytruda" class=" ctxTooltipCard" data-jalios-id='pprd_2982864'>KEYTRUDA
                </a></h3>
                <div class="layerInfo">
                    <div class="typesAndDate">
                    <span class="types">Medicine</span>
                        <span class="date">-
                        Posted on
                        27/05/2024

                    </span>
                    </div>
                </div>
            </div>
            <div class="actions">
```

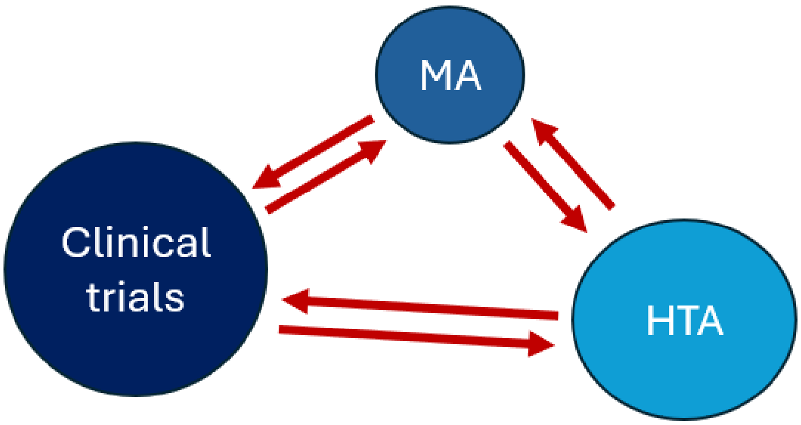
```
<li class="default-grey avisImportantClass ">

    <div class="date-avis">3/27/24</div>
    <a href="jcms/p_3508492/en/keytruda-pembrolizumab-cancer-des-voies-biliaires" class=" ctxTooltipCard" data-jalios-id='p_3508492'><h3>KEYTRUDA (pembrolizumab) -
    <div class="extrait-avis">
        <a href="jcms/p_3508492/en/keytruda-pembrolizumab-cancer-des-voies-biliaires" class=" ctxTooltipCard" data-jalios-id='p_3508492'>

            Extension d'indication. L'essentiel Avis favorable au remboursement dans l'indication KEYTRUDA en association à la gemcitabi...
        </a>
    </div>

        <div class="level-avis">
            <span>CAV :</span>
            <div class="barra-level">
                <span class="selected">5</span><span class="selected">4</span><span class="">3</span><span class="">2</span><span class="">1</span>
            </div>
        </div>


    <div class="link-all">
        <a href="jcms/p_3508492/en/keytruda-pembrolizumab-cancer-des-voies-biliaires" class=" link-arrow ctxTooltipCard" data-jalios-id='p_3508492'>
            <span class="hidden">icône flèche</span>
        </a>
    </div>
</li>
```

```
library(rvest)
library(dplyr)


# List of user agents
user_agents <- c(
  'Mozilla/5.0 (Windows NT 10.0; Win64; x64) AppleWebKit/537.36 (KHTML, like Gecko) Chrome/123.0.0.1 Safari/537.36',
  'Mozilla/5.0 (Windows NT 10.0; Win64; x64) AppleWebKit/537.36 (KHTML, like Gecko) Chrome/123.0.0.2 Safari/537.36',
  'Mozilla/5.0 (Windows NT 10.0; Win64; x64; rv:99.0) Gecko/20100101 Firefox/99.0',
  'Mozilla/5.0 (Windows NT 10.0; Win64; x64; rv:98.0) Gecko/20100101 Firefox/98.0',
  'Mozilla/5.0 (Macintosh; Intel Mac OS X 10_15_7) AppleWebKit/605.1.15 (KHTML, like Gecko) Version/14.1 Safari/605.1.15',
  'Mozilla/5.0 (Windows NT 10.0; Win64; x64) AppleWebKit/537.36 (KHTML, like Gecko) Chrome/121.0.0.0 Safari/537.36'
)

# Function to get a random user agent
get_random_user_agent <- function() {
  sample(user_agents, 1)
}

# Function to generate a request with random user agent
request_generator <- function(url, timeout = 30) {
  # Select a random user agent
  user_agent <- get_random_user_agent()

  # Configure the HTTP GET request with the selected user agent
  response <- RETRY("GET", url, user_agent(user_agent), timeout(timeout), quiet = TRUE)

  return(response)
}
```

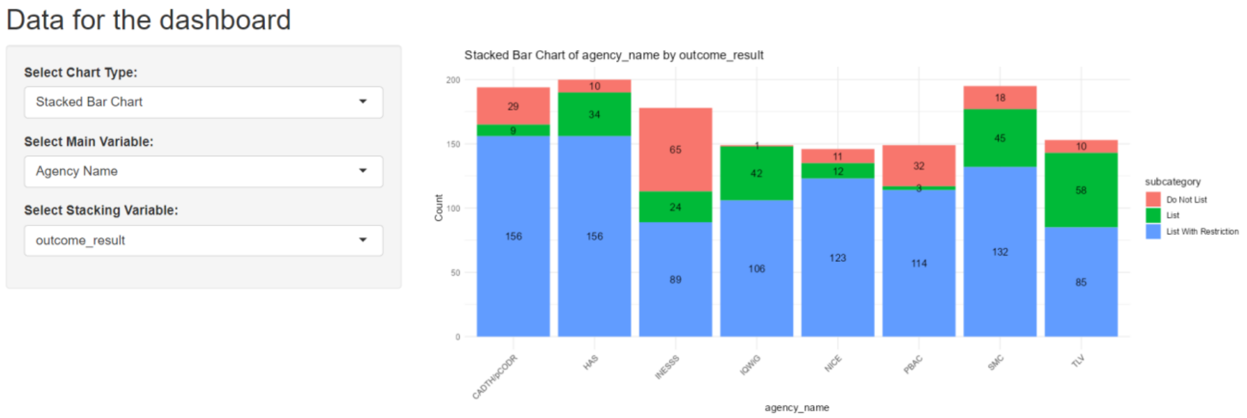
```
# Base URL (add page numbers)
base_url <- 'https://www.has-sante.fr/jcms/fc_2875171/en/resultat-de-recherche?text=&tmpParam=typesf%3Dtechnologies%2Fgenerated.Medicament&typesf=technologies%2Fgenerated.Medicament&opSearch=&portal=prd1_2986155&page='

# Initializing an empty list to store the data
data_list <- list()

# Looping through pages 1 to 12
```

```r
for (page_num in 1:12) {
  # Construct the URL for the current page
  url <- paste0(base_url, page_num, '&replies=100')

  # Read the HTML content from the webpage
  webpage <- read_html(url)

  # Extract all items that match the class "itResultat"
  items <- webpage %>% html_nodes('.itResultat')

  # Loop through each item to extract the required information
  for (i in seq_along(items)) {
    item <- items[i]

    # Extract the URL
    item_url <- item %>% html_node('.title a') %>% html_attr('href')

    # Extract the title
    title <- item %>% html_node('.title a') %>% html_text(trim = TRUE)

    # Extract the posted date
    posted_date <- item %>% html_node('.date') %>% html_text(trim = TRUE) %>%
      gsub("Posted on", "", .) %>% trimws()

    # Append the data to the list
    data_list <- append(data_list, list(data.frame(
      URL = item_url,
      Title = title,
      Posted_Date = posted_date,
      stringsAsFactors = FALSE
    )))
  }
}

# Combine the list into a single data frame
final_data <- bind_rows(data_list)
```

Matching data is challenging



Data Exploration

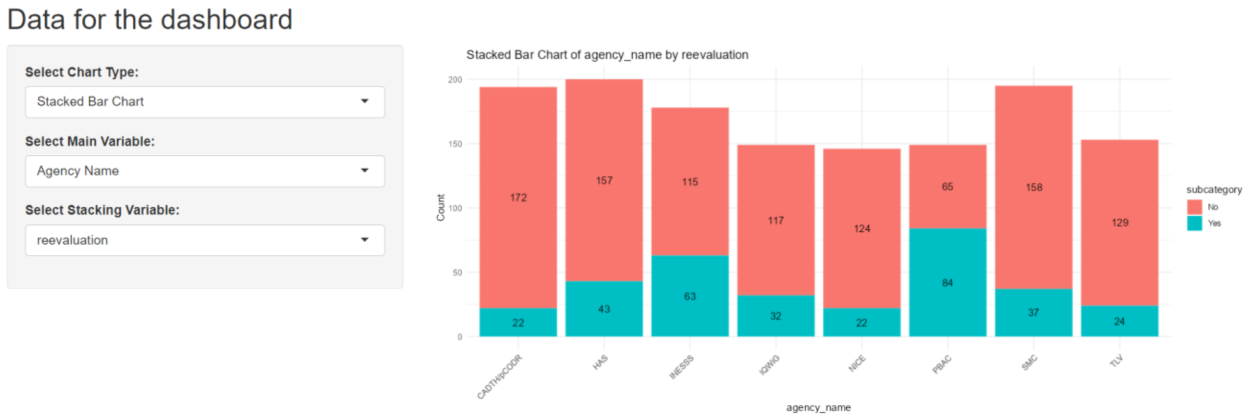


Data for the dashboard

Select Chart Type: Stacked Bar Chart

Select Main Variable: Agency Name

Select Stacking Variable: outcome_result

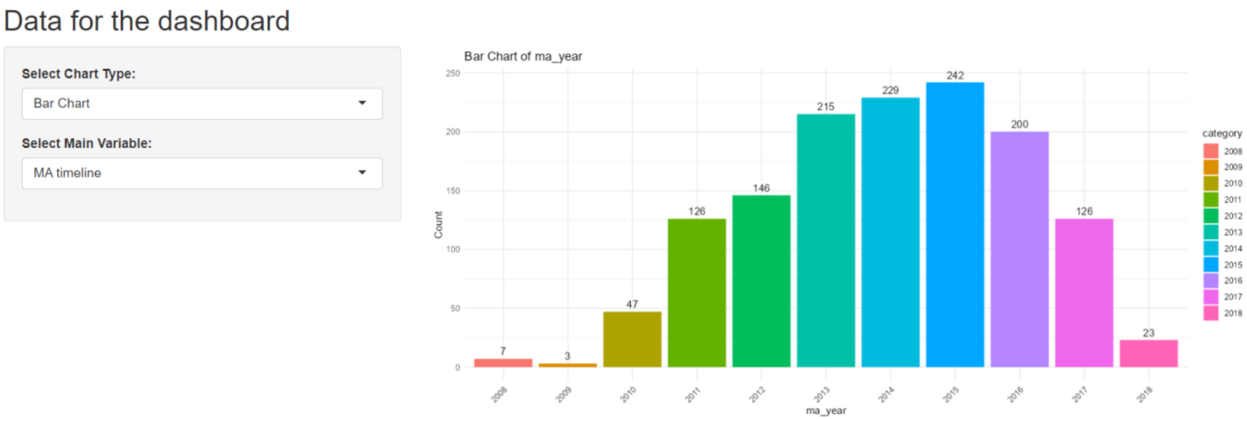


Data for the dashboard

Select Chart Type: Stacked Bar Chart

Select Main Variable: Agency Name

Select Stacking Variable: reevaluation



Data for the dashboard

Select Chart Type: Bar Chart

Select Main Variable: MA timeline

```
## Rows: 1,364
## Columns: 23
## $ agency_name                 <chr> "CADTH/pCODR", "HAS", "INESSS",
"PBAC", "…
## $ molecule_name               <chr> "Budesonide", "Budesonide",
"Budesonide",…
## $ ma_date                     <chr> "2016-06-20", "2016-06-23", "2016-06-
20",…
## $ outcome_date                <chr> "2017-05-22", "2017-01-25", "2017-02-
01",…
## $ timetoHTA                   <int> 336, 216, 226, 684, 78, 41, 133, 118,
333…
## $ approval_type               <chr> "Standard", "Standard", "Standard",
"Stan…
## $ orphan_designation          <chr> "Not Orphan", "Not Orphan", "Not
Orphan",…
## $ reevaluation                <chr> "No", "No", "No", "No", "Yes", "No",
"No"…
## $ outcome_result              <chr> "Do Not List", "List With
Restriction", "…
```

```
## $ clinical_endpoint_considered <chr> "Yes", "No", "Yes", "No", "No", "No",
"No…
## $ Approved                     <int> 0, 1, 0, 0, 1, 1, 1, 1, 0, 1, 1, 1,
0, 1,…
## $ trial_identifier             <chr> "NCT00679380", "NCT00679380",
"NCT0067938…
## $ therapeutic_area             <chr> "Gastroenterology",
"Gastroenterology", "…
## $ atc_code                     <chr> NA, "A07EA06", NA, NA, "A07EA06", NA,
NA,…
## $ time_from_CT_to_MA           <int> 2912, 2915, 2912, 2618, 2915, 2614,
1905,…
## $ time_from_CT_to_HTA          <int> 3248, 3131, 3138, 3302, 2993, 2655,
2038,…
## $ cancer                       <chr> "Not Cancer", "Not Cancer", "Not
Cancer",…
## $ ma_year                      <int> 2016, 2016, 2016, 2015, 2016, 2016,
2014,…
## $ hta_year                     <int> 2017, 2017, 2017, 2017, 2016, 2015,
2014,…
## $ start_date                   <chr> "2008-06-30", "2008-06-30", "2008-06-
30",…
## $ phase                        <chr> "Phase 3", "Phase 3", "Phase 3",
"Phase 3…
## $ allocation                   <chr> "Randomized", "Randomized",
"Randomized",…
## $ conditions                   <chr> "Ulcerative Colitis", "Ulcerative
Colitis…
```

Model Overview

Purpose: To analyse the time-to-event data for drug approvals and visualise the duration between key milestones

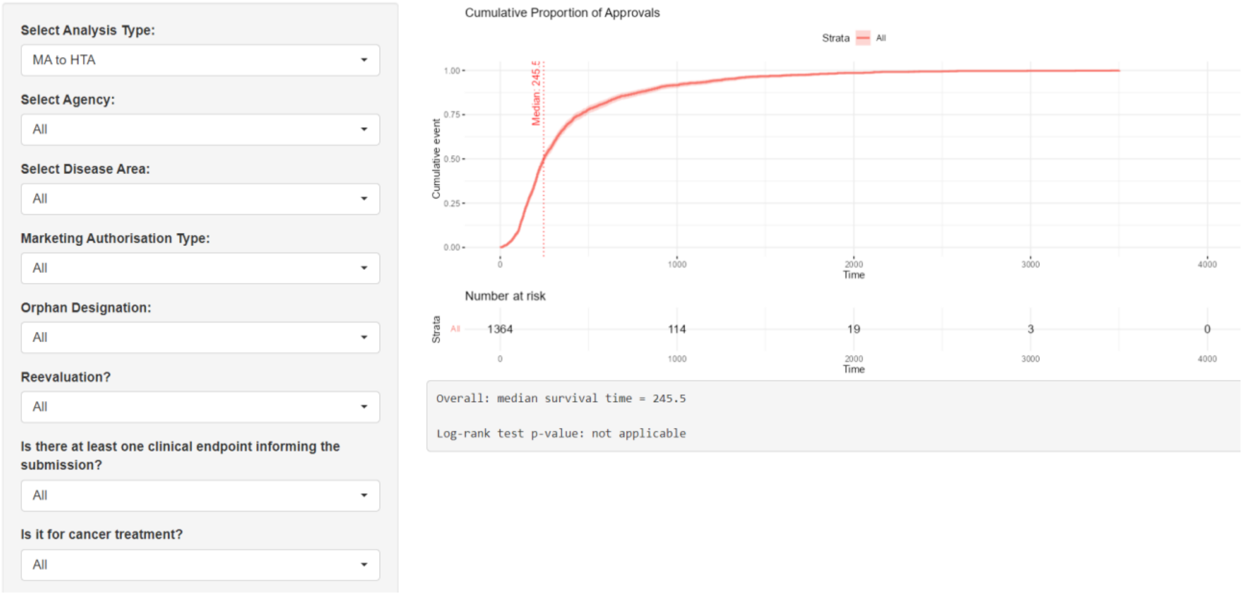
Data Input: User-selected filters and options, such as agency, disease area, and whether to remove censoring.

Method: Kaplan-Meier model

Time: Days

Censoring: The model can include or exclude censored data (rejections)

Comparison: Log-rank test and median survival times



Select Analysis Type: MA to HTA

Select Agency: All

Select Disease Area: All

Marketing Authorisation Type: All

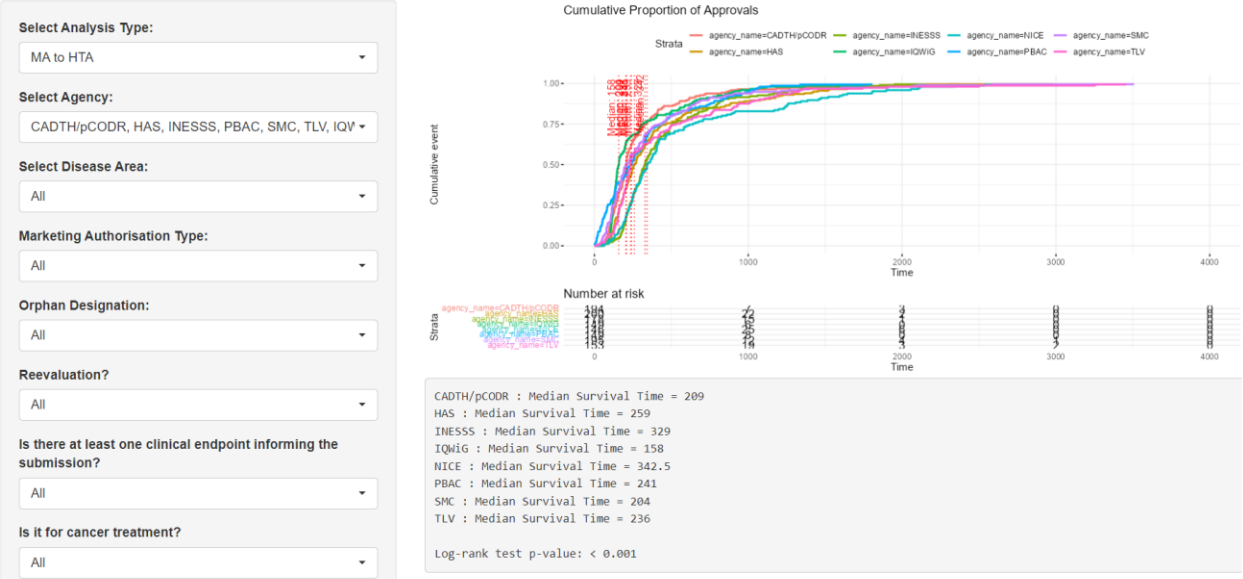
Orphan Designation: All

Reevaluation? All

Is there at least one clinical endpoint informing the submission? All

Is it for cancer treatment? All

```
Overall: median survival time = 245.5

Log-rank test p-value: not applicable
```



Select Analysis Type: MA to HTA

Select Agency: CADTH/pCODR, HAS, INESSS, PBAC, SMC, TLV, IQV

Select Disease Area: All

Marketing Authorisation Type: All

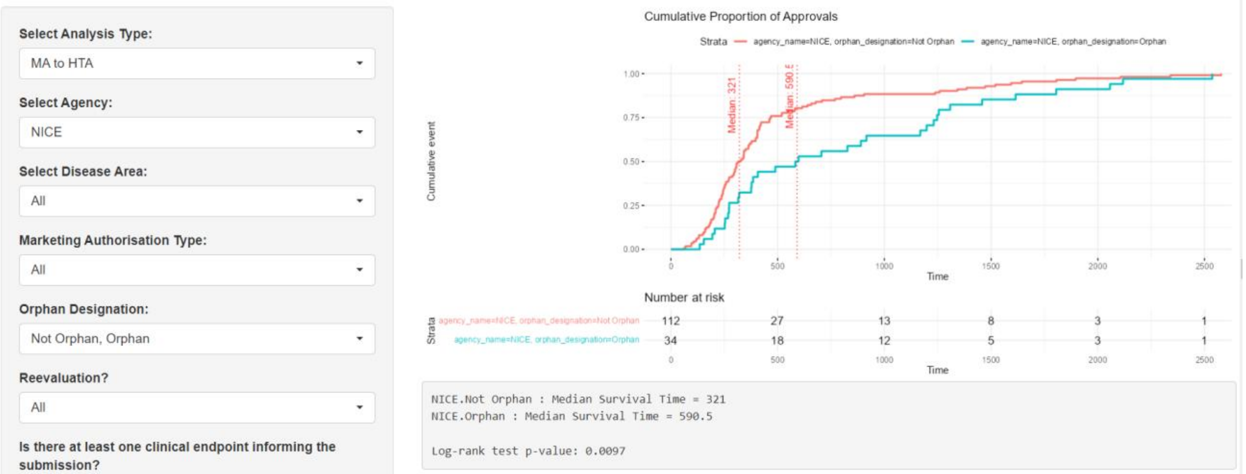
Orphan Designation: All

Reevaluation? All

Is there at least one clinical endpoint informing the submission? All

Is it for cancer treatment? All

```
CADTH/pCODR : Median Survival Time = 209
HAS : Median Survival Time = 259
INESSS : Median Survival Time = 329
IQWiG : Median Survival Time = 158
NICE : Median Survival Time = 342.5
PBAC : Median Survival Time = 241
SMC : Median Survival Time = 204
TLV : Median Survival Time = 236

Log-rank test p-value: < 0.001
```



Select Analysis Type: MA to HTA

Select Agency: NICE

Select Disease Area: All

Marketing Authorisation Type: All

Orphan Designation: Not Orphan, Orphan

Reevaluation? All

Is there at least one clinical endpoint informing the submission?

Cumulative Proportion of Approvals
Strata
agency_name=NICE, orphan_designation=Not Orphan
agency_name=NICE, orphan_designation=Orphan
Cumulative event
1.00
0.75
0.50
0.25
0.00
Median: 321
Median: 590.5
0
500
1000
1500
2000
2500
Time
Number at risk
Strata
agency_name=NICE, orphan_designation=Not Orphan
112
27
13
8
3
1
agency_name=NICE, orphan_designation=Orphan
34
18
12
5
3
1
0
500
1000
1500
2000
2500
Time

```
NICE.Not Orphan : Median Survival Time = 321
NICE.Orphan : Median Survival Time = 590.5

Log-rank test p-value: 0.0097
```

Code

```
library(shiny)
library(shinyWidgets)
library(survival)
library(survminer)
```

1. UI

```
#### UI ####
ui5 <- fluidPage(
  titlePanel("Timeline Analysis Dashboard"),
  sidebarLayout(
    sidebarPanel(
      pickerInput("selected_analysis_type", "Select Analysis Type:",
                  choices = c("MA to HTA", "Trial to MA", "Trial to HTA"),
                  selected = "MA to HTA",
                  multiple = FALSE),
      pickerInput("selected_agencies", "Select Agency:",
                  choices = c("All", unique(data$agency_name)),
                  selected = "All",
                  multiple = TRUE,
                  options = list(`actions-box` = TRUE, `live-search` =
TRUE)),
      pickerInput("selected_disease_areas", "Select Disease Area:",
                  choices = c("All", unique(data$therapeutic_area)),
                  selected = "All",
                  multiple = TRUE,
                  options = list(`actions-box` = TRUE, `live-search` =
TRUE)),
      pickerInput("selected_ma_type", "Marketing Authorisation Type:",
                  choices = c("All", unique(data$approval_type)),
                  selected = "All",
                  multiple = TRUE,
                  options = list(`actions-box` = TRUE, `live-search` =
TRUE)),
      pickerInput("selected_orphan", "Orphan Designation:",
                  choices = c("All", unique(data$orphan_designation)),
                  selected = "All",
                  multiple = TRUE,
                  options = list(`actions-box` = TRUE, `live-search` =
TRUE)),
      pickerInput("selected_evaluation", "Reevaluation?",
                  choices = c("All", unique(data$reevaluation)),
                  selected = "All",
                  multiple = TRUE,
                  options = list(`actions-box` = TRUE, `live-search` =
TRUE)),
      pickerInput("selected_endpoint", "Is there at least one clinical
endpoint informing the submission?",
                  choices = c("All",
unique(data$clinical_endpoint_considered)),
                  selected = "All",
                  multiple = TRUE,
                  options = list(`actions-box` = TRUE, `live-search` =
TRUE)),
      pickerInput("selected_cancer", "Is it for cancer treatment?",
                  choices = c("All", unique(data$cancer)),
                  selected = "All",
                  multiple = TRUE,
                  options = list(`actions-box` = TRUE, `live-search` =
TRUE)),
      pickerInput("selected_outcome", "Any reimbursement restrictions?",
                  choices = c("All", unique(data$outcome_result)),
                  selected = "All",
                  multiple = TRUE,
                  options = list(`actions-box` = TRUE, `live-search` =
TRUE)),
      pickerInput("remove_censoring", "Censor rejections?",
                  choices = c("Do", "Don't"),
                  selected = "Don't",
                  multiple = FALSE),
      hr(),
      helpText("Select stratification variables to display survival plots.")
    ),
    mainPanel(
      plotOutput("survivalPlot"),
      verbatimTextOutput("meanSurvivalTime")
    )
  )
)
```

2. Server

```
server <- function(input, output) {
  .....
}
```

3. Filter the dataset based on user-selected criteria

The code checks each input filter and applies it to the dataset. If an input is NULL or set to “All”, the filter is not applied (TRUE) - include all rows. Otherwise, it filters the data based on the selected values.

```
filtered_data <- reactive({ #REACTIVE ensures that the filtered data is
updated reactively whenever the user changes the input selections
  data %>%
    filter(
      if (is.null(input$selected_agencies) | "All" %in%
input$selected_agencies) TRUE else agency_name %in% input$selected_agencies,
      if (is.null(input$selected_disease_areas) | "All" %in%
input$selected_disease_areas) TRUE else therapeutic_area %in%
input$selected_disease_areas,
      if (is.null(input$selected_ma_type) | "All" %in%
input$selected_ma_type) TRUE else approval_type %in% input$selected_ma_type,
      if (is.null(input$selected_orphan) | "All" %in% input$selected_orphan)
TRUE else orphan_designation %in% input$selected_orphan,
      if (is.null(input$selected_evaluation) | "All" %in%
input$selected_evaluation) TRUE else reevaluation %in%
input$selected_evaluation,
      if (is.null(input$selected_endpoint) | "All" %in%
input$selected_endpoint) TRUE else clinical_endpoint_considered %in%
input$selected_endpoint,
      if (is.null(input$selected_cancer) | "All" %in% input$selected_cancer)
TRUE else cancer %in% input$selected_cancer,
      if (is.null(input$selected_outcome) | "All" %in%
input$selected_outcome) TRUE else outcome_result %in% input$selected_outcome
    )
})
```

4. Kaplan-Meier Analysis

```
km_analysis <- reactive({
  ...
})
```

4.1 Data Filtering and Initialization

Retrieves the filtered data. If the filtered data has no rows, return a list with NULL values to indicate there’s no data to analyze.

```
  data <- filtered_data()

  if (nrow(data) == 0) {
    return(list(
      km_fit = NULL,
      median_surv = NULL,
      stratification_vars = NULL,
      time_var = NULL,
      data = NULL
    ))
  }
```

4.2 Check if Censoring Should Be Removed

If censoring should be removed, it changes the Approved status of censored data points (Approved == 0) to 1.

```
  if (!is.null(input$remove_censoring) && input$remove_censoring == "Don't")
{
    data$Approved <- ifelse(data$Approved == 0, 1, data$Approved)
  }
```

4.3 Determine Stratification Variables

Adds the selected stratification variables to the stratification_vars vector.

```
  stratification_vars <- c()
  if (!is.null(input$selected_agencies) && !("All" %in%
input$selected_agencies)) stratification_vars <- c(stratification_vars,
"agency_name")
  if (!is.null(input$selected_disease_areas) && !("All" %in%
input$selected_disease_areas)) stratification_vars <- c(stratification_vars,
"therapeutic_area")
  if (!is.null(input$selected_ma_type) && !("All" %in%
input$selected_ma_type)) stratification_vars <- c(stratification_vars,
"approval_type")
  if (!is.null(input$selected_orphan) && !("All" %in% input$selected_orphan))
stratification_vars <- c(stratification_vars, "orphan_designation")
  if (!is.null(input$selected_evaluation) && !("All" %in%
input$selected_evaluation)) stratification_vars <- c(stratification_vars,
"reevaluation")
  if (!is.null(input$selected_endpoint) && !("All" %in%
input$selected_endpoint)) stratification_vars <- c(stratification_vars,
"clinical_endpoint_considered")
  if (!is.null(input$selected_cancer) && !("All" %in% input$selected_cancer))
stratification_vars <- c(stratification_vars, "cancer")
  if (!is.null(input$selected_outcome) && !("All" %in%
input$selected_outcome)) stratification_vars <- c(stratification_vars,
"outcome_result")
```

4.4 Determine Time Variable Based on Selected Analysis Type

Sets the time_var based on the type of analysis selected by the user.

```
  time_var <- switch(input$selected_analysis_type,
                     "MA to HTA" = "timetoHTA",
                     "Trial to MA" = "time_from_CT_to_MA",
                     "Trial to HTA" = "time_from_CT_to_HTA")
```

4.5 Formula for Survival Analysis

If there are stratification variables, they are included in the formula. If no stratification variables are selected, the formula includes only the time variable and the approval status.

```
  formula <- if (length(stratification_vars) > 0) {
    as.formula(paste("Surv(", time_var, ", Approved) ~",
paste(stratification_vars, collapse = " + ")))
  } else {
```

```r
    as.formula(paste("Surv(", time_var, ", Approved) ~ 1"))
  }
```

4.6 Kaplan-Meier Fit

Fits the Kaplan-Meier model using the constructed formula and the filtered data. Stores the formula used in the model fit for reference.

```r
  km_fit <- survfit(formula, data = data)
  km_fit$call$formula <- formula
```

4.7 Calculate Median Survival Time

If there are stratification variables, it calculates the median survival time for each stratum separately. If no stratification variables are present, it calculates the median survival time for the entire dataset.

```r
  if (length(stratification_vars) > 0) {

    median_surv <- sapply(levels(interaction(data[, stratification_vars, drop
= TRUE])), function(strata) {

      group_data <- data[interaction(data[, stratification_vars, drop =
TRUE]) == strata, ]

      fit_strata <- survfit(Surv(as.numeric(group_data[[time_var]]),
group_data$Approved) ~ 1, data = group_data)

      summary(fit_strata)$table["median"]

    }, simplify = FALSE)

  } else {

    median_surv <- summary(km_fit)$table["median"]
  }
```

4.8 Return Results

```r
  list(
    km_fit = km_fit,
    median_surv = median_surv,
    stratification_vars = stratification_vars,
    time_var = time_var,
    data = data
  )
})
```

5. Survival Plot

5.1 Prepare Data and Fit Model

```
  output$survivalPlot <- renderPlot({
    analysis <- km_analysis()
    km_fit <- analysis$km_fit
    median_surv <- analysis$median_surv
    stratification_vars <- analysis$stratification_vars
    time_var <- analysis$time_var
    data <- analysis$data

    if (is.null(km_fit)) {
      plot.new()
      text(0.5, 0.5, "No data to display.", cex = 1.5)
      return(NULL)
    }
```

5.2 Generate Kaplan-Meier Plot

```
    plot_title <- "Cumulative Proportion of Approvals"

    p <- ggsurvplot(km_fit, data = data, risk.table = TRUE,
                    ggtheme = theme_minimal(),
                    title = plot_title,
                    fun = "event")
```

5.3 Add Median Survival Lines

```
      if (length(stratification_vars) > 0) {
    for (strata in names(median_surv)) {
      median_time <- median_surv[[strata]]
      p$plot <- p$plot + geom_vline(xintercept = median_time, linetype =
"dotted",
                                    color = "red") +
        annotate("text", x = median_time, y = 0.5, label = paste("Median:",
round(median_time, 1)),
                 angle = 90, vjust = -0.5, hjust = -0.5, color = "red")
    }
  }

      # Handling non-stratified data
        else {
    median_time <- median_surv
    p$plot <- p$plot + geom_vline(xintercept = median_time, linetype =
"dotted",
                                  color = "red") +
      annotate("text", x = median_time, y = 0.5, label = paste("Median:",
round(median_time, 1)),
               angle = 90, vjust = -0.5, hjust = -0.5, color = "red")
  }
```

```
    print(p)
  })
```

6. Text box

6.1 Prepare Data and Fit Model

```
output$meanSurvivalTime <- renderText({
  analysis <- km_analysis()
  median_surv <- analysis$median_surv
  stratification_vars <- analysis$stratification_vars
  data <- analysis$data

  if (is.null(data) || nrow(data) == 0) {
    return("No data to display.")
  }
```

6.2 Calculate Median Survival Times

```
  median_list <- list()

  if (length(stratification_vars) > 0) {
    for (group in names(median_surv)) {
      median_list <- c(median_list, paste(group, ": Median Survival Time =",
median_surv[[group]]))
    }
      }
  else {
    median_list <- c(median_list, paste("Overall: median survival time =",
median_surv))
  }
```

6.3 Log-Rank Test and Final Text

```
    # check stratification variables and unique values

    if (length(stratification_vars) > 0 && any(sapply(data[,
stratification_vars, drop = FALSE], function(x) length(unique(x))) > 1)) {

    # log rank test

    lr_test <- survdiff(as.formula(paste("Surv(", analysis$time_var, ",
Approved) ~", paste(stratification_vars, collapse = " + "))), data = data)

    # p-value

    p_value <- 1 - pchisq(lr_test$chisq, length(lr_test$n) - 1)
    if (p_value < 1e-3) {
      p_value <- "< 0.001"
    } else {
      p_value <- round(p_value, 4)
    }
    p_value_text <- paste("Log-rank test p-value:", p_value)
  } else {
    p_value_text <- "Log-rank test p-value: not applicable"
  }

    # Return text

    final_text <- paste(c(median_list, "", p_value_text), collapse = "\n")

    return(final_text)
  })
}
```

Run!

```
shinyApp(ui = ui, server = server)
```

Next steps:

1. Full data
2. Additional drug development time steps
3. Influence of factors on the timelines
4. Predictive analytics

Thank you for attention!

Email: v.zaitceva@hiveoptimum.com
LinkedIn: Victoria Zaitceva

HTAHive