Modeling the Future: Pioneering the First Dossier Submission with R

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BMS: Sven Klijn & Jason Foo
National Health Care Institute (ZIN): Mohamed El Alili & Joost Enzing

Bristol Myers Squibb®

Zorginstituut Nederland

Background to the use of Excel within ZIN

- **Benefits of Excel**
  - User-friendliness, intuitive
  - Familiarity
  - Sufficient in many cases

- **Drawbacks of Excel**
  - Increasing complexity (error checking, transparency)
  - Long running times
  - Large VBA script
  - For some models infeasible

- **Potential of R**
  - → *If properly implemented. Barriers exist!*

Project objective

– To facilitate the possibility to submit models in R to ZIN by developing and pilot-testing submission guidance

Steps taken since October 2021

– Spoken to international consortia (DARTH and R for HTA)

– Linked up with other HTA organizations (WG HTA and R)

– Published a guideline for R models

– Performed a pilot with BMS

– Worked on our IT infrastructure to allow (safe) use of R (Posit Workbench, includes other languages such as Python)

Pilot

– Aim was to gain experience in cost-effectiveness models in R to:

  – Identify barriers and facilitators
  – Improve the guideline

Further:

  – Everything similar to when a model in Excel is submitted

Inclusion criteria pilot

– Submission of dossier between april 2022 and april 2024

– Full assessment → includes a CE-model

– Oncology, partitioned survival model

– Frequent meetings between registration holder and ZIN

Results pilot

– BMS entered the pilot:

  – Lisocabtagene maraleucel (Breyanzi®) for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy
  – Partitioned survival model built in R following the guideline
  – Submitted 13 february 2024

Take home messages ZIN

- Preconditions:

    - Support from organization
    - Safe and secure environment within the IT infrastructure of the organization
    - Sufficient knowledge of R within the organization (courses etc.)

- Important:

    - Standardization
    - **Collaboration** and **alignment** between HTA organizations
    - Willingness of pharmaceutical companies to submit models in R
    - Academic consortia should reach out to HTA organizations and ask their input on the guidelines or tools they develop

Model overview

Model overview for Breyanzi in 2L LBCL

| Population	Intervention	Comparators	Outcomes	Settings
Adults with relapse/refractory LBCL i.e., those who are refractory or relapsed in <12 months following frontline therapy and intended for SCT	Breyanzi	**Standard of care** Salvage chemotherapy (R-GDP, R-ICE, R-DHAP) **+** HDCT (high-dose chemotherapy) **+** ASCT (Autologous Stem Cell Therapy)	• Life Years (LYs) • Quality-adjusted LYs (QALYs) • Costs by category • ICER • Net monetary benefit	**Perspective:** Healthcare and societal **Annual discount** Health: 1.5% Cost: 4.0% **Time horizon:** Lifetime (flexibility for shorter time horizons)

LBCL: Large B-Cell Lymphoma; R-DHAP, Rituximab, Dexamethasone, Cytarabine, and Cisplatin; R-GDP, Rituximab, Gemcitabine, Dexamethasone, and Cisplatin; R-ICE, Rituximab, Ifosfamide, Carboplatin, Etoposide; SCT, Stem Cell Transplant;

Model structure

Partitioned survival analysis closely reflects observed clinical trial data and captures disease pathway with the following health states:
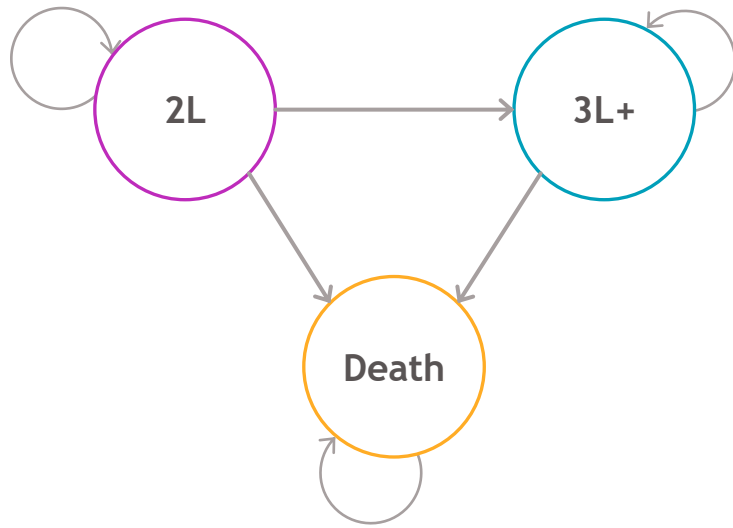
- Time in EFS captures the second-line health state (2L EFS)
- Patients can die from either the 2L EFS or 3L+ states
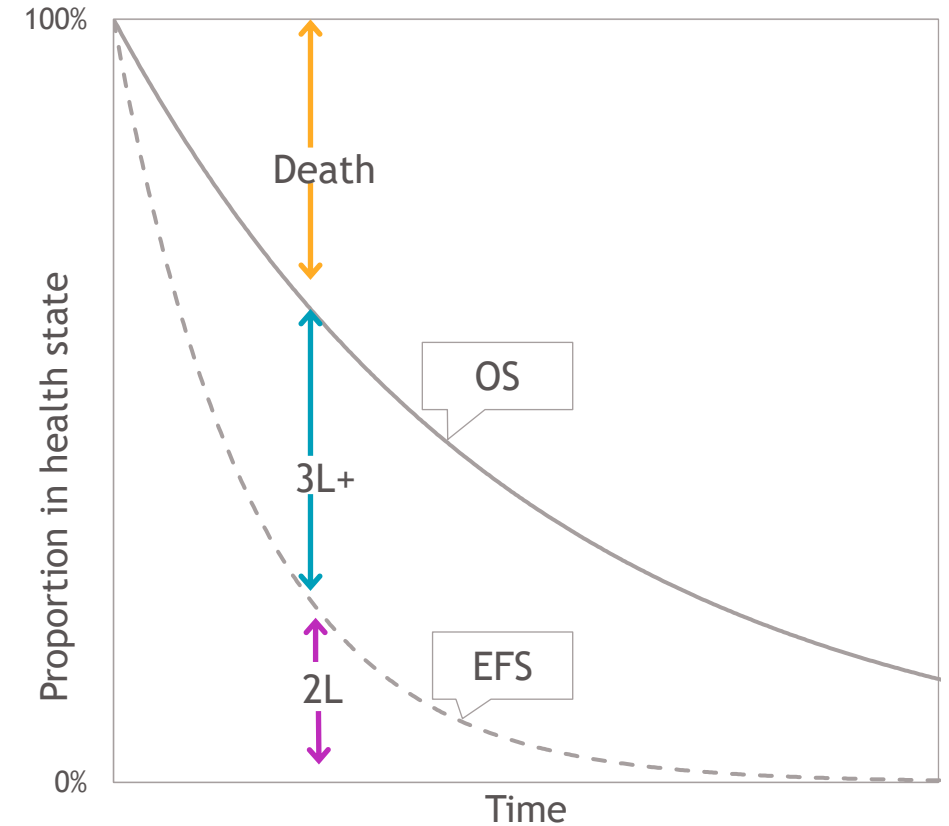- OS is extrapolated from the trial using a mixture cure model

Image is for illustrative purposes only and does not reflect actual data

2L, second line, 3L+, third line and above, EFS, event free survival, LBCL, Large B-cell lymphomas OS, overall survival

Technical aspects

Packages used in the model

Analyses

- dampack: Analyses (PSA)
- flexsurv: Survival extrapolations
- mvtnorm: Statistical distributions
- MASS: Data wrangling
- reshape2: Data wrangling

Presentation

- kableExtra: Table outputs
- gridExtra: Graphs
- ggplot2: Graphs
- scales: Graphs
- testthat: Unit testing

File structure

- Data
- Functions
- Testing (unit tests)
- Markdown files (html, Rmd, Rproj)

Structure of the R-model: Data files

📁 Graph data
- KM data

📁 General population
- Mortality
- Utility

📁 PAID
- Unrelated medical costs

📁 Statistical fits
- Survival extrapolation parameters
- Health state utilities

📄 Drug costs

📄 Drug regimens

📄 Other (e.g., patient characteristics, safety, unit costs)

📄 Scenario inputs

Structure of the R-model: Function files

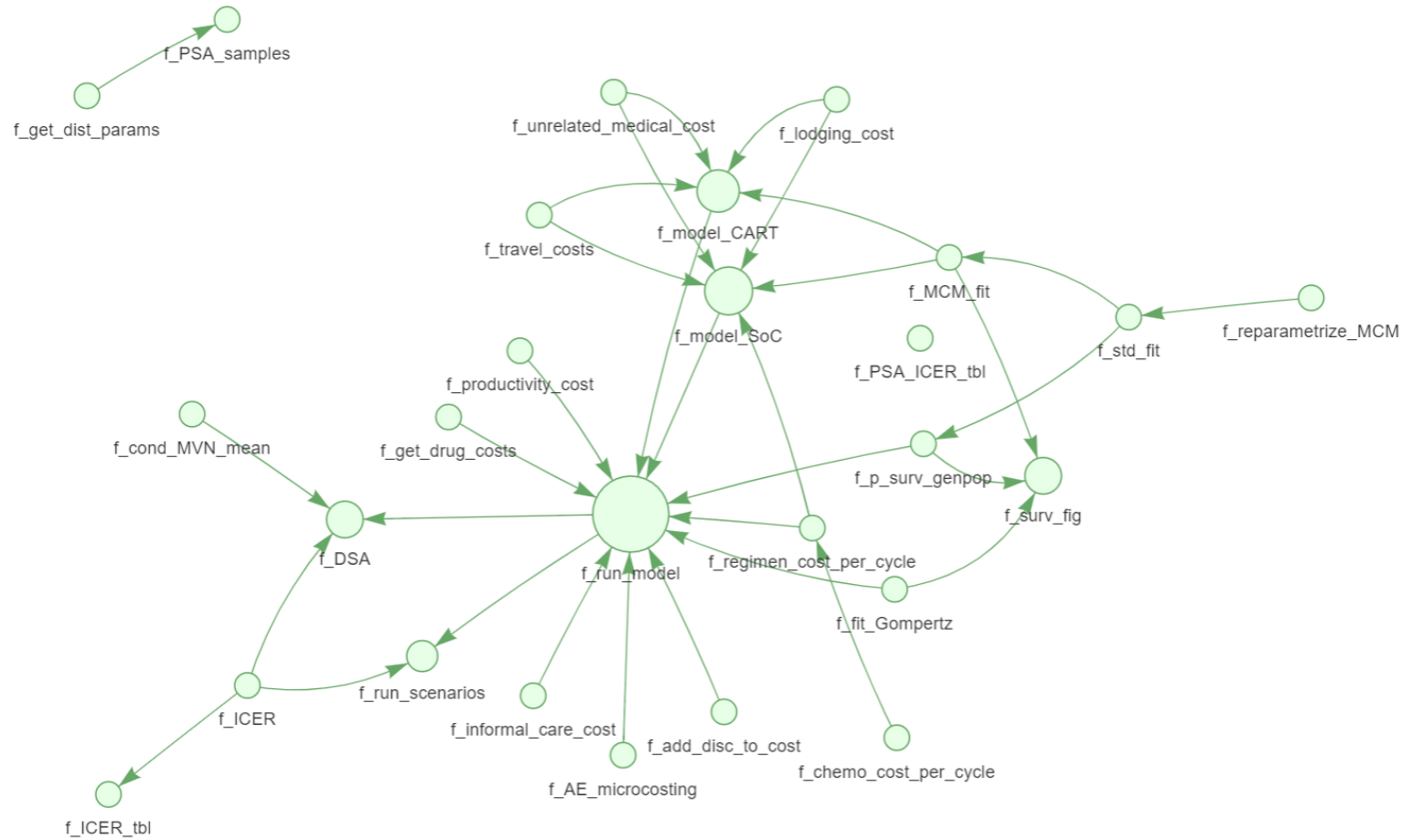**Core**
- Engine
- Survival
- Costs
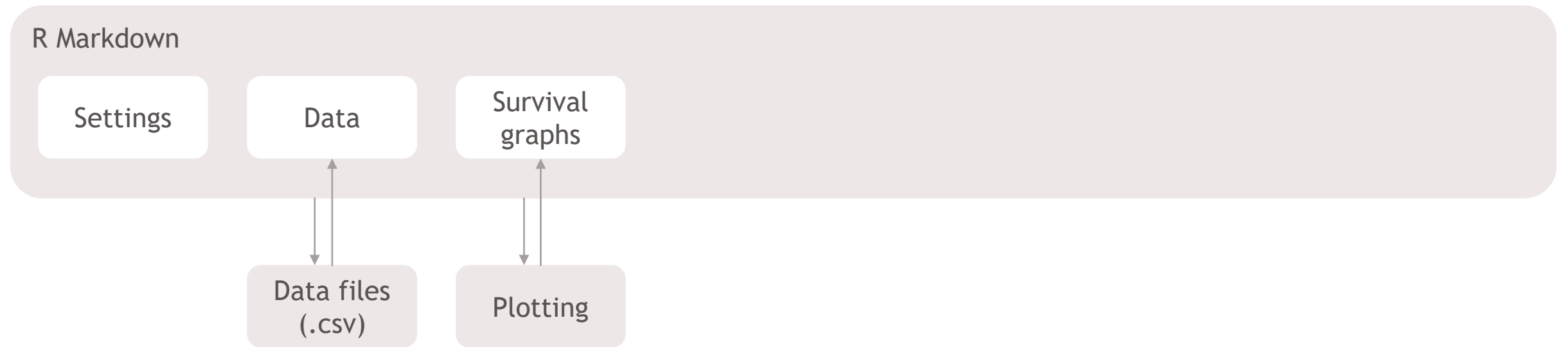
Sensitivity
- Scenarios
- Sensitivity

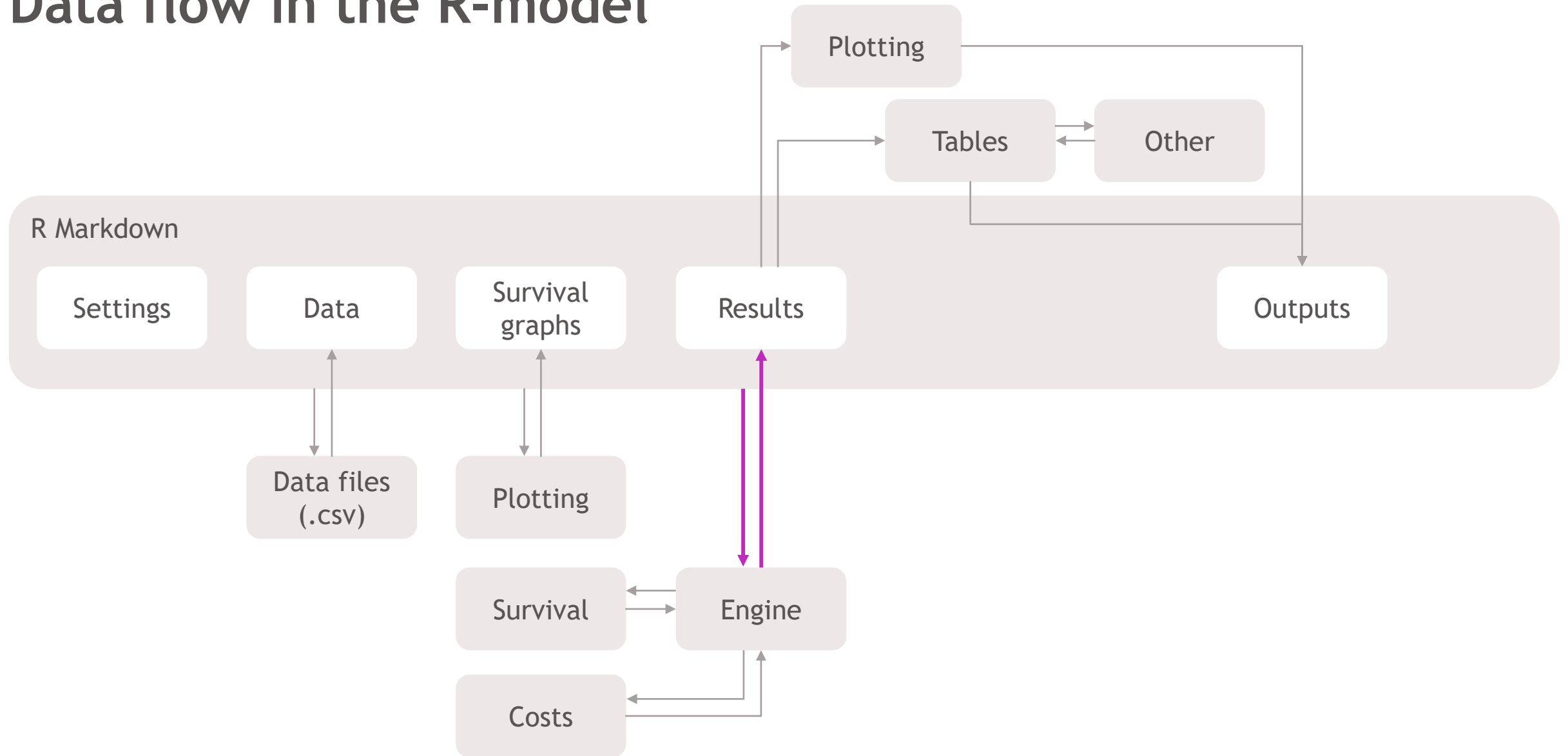**Formatting**
- Plotting
- Tables
- Other (ICER calculation)

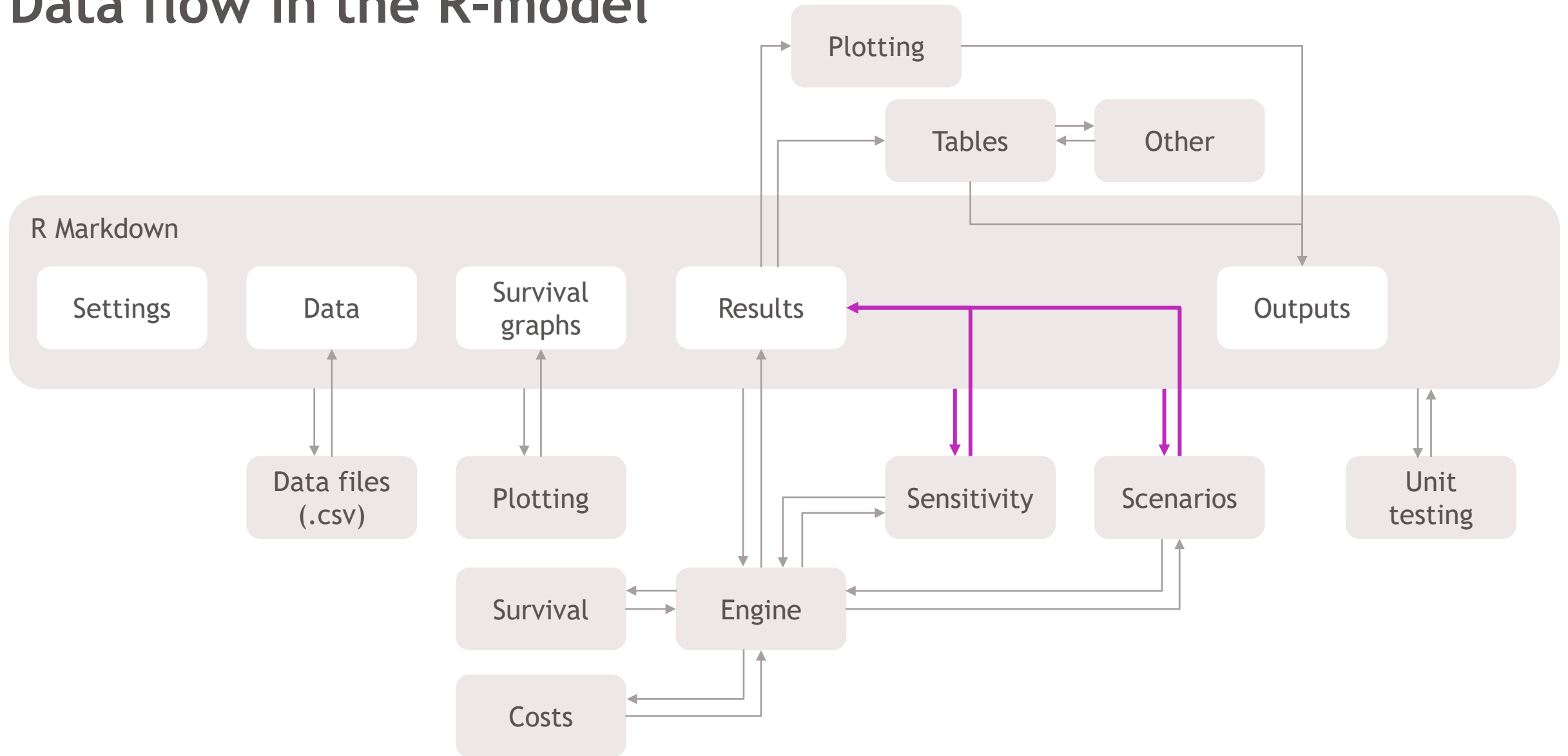# Structure of the R-model: visualization of Core functions
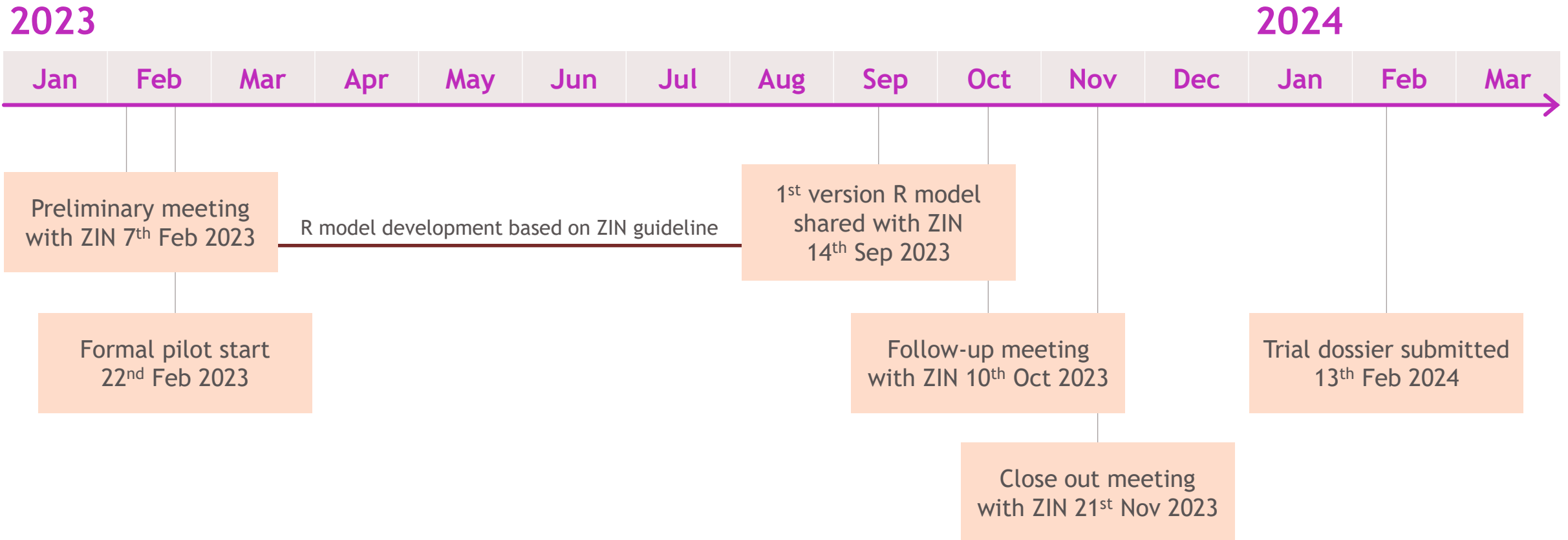
Data flow in the R-model

R Markdown

Settings

Data

Survival graphs

Data files (.csv)

Plotting

Data flow in the R-model

Data flow in the R-model

ZIN pilot interactions/timelines

2023　　　　　　　　　　　　　　　　　　　　　　　　　　**2024**

Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar

Preliminary meeting
with ZIN 7th Feb 2023

R model development based on ZIN guideline

1st version R model
shared with ZIN
14th Sep 2023

Formal pilot start
22nd Feb 2023

Follow-up meeting
with ZIN 10th Oct 2023

Trial dossier submitted
13th Feb 2024

Close out meeting
with ZIN 21st Nov 2023

ZIN – National Health Care Institute, ISPOR – International Society for Pharmacoeconomics and Outcomes Research

Key takeaways/learnings (1)

Advantages of using R:
- Greater transparency
- Faster model run time
- Smaller file sizes
- Better graphics
- Reusability
- Integration options with other software

Ensure that basic technical requirements are met/agreed at the outset
- Correct software versions/packages installed/agreed

Use of external packages provides benefits but also introduces risks
- Convenient
- Common ground for multi-stakeholder interactions
- Potential security concerns
- (Lack of) maintenance can be a challenge

Valuable having the same vendor for the Excel and R models
- Allowed for cross-validation

Key takeaways/learnings (2)

Sufficient opportunities for touchpoints with ZIN during the pilot

ZIN guidelines were clear and easy to follow

Not all companies/vendors have expertise in modelling in R
- Limits choice of vendors

Broader adoption of R models for HTA submissions is necessary in order to make this attractive for manufacturers to transition away from Excel

Thank you