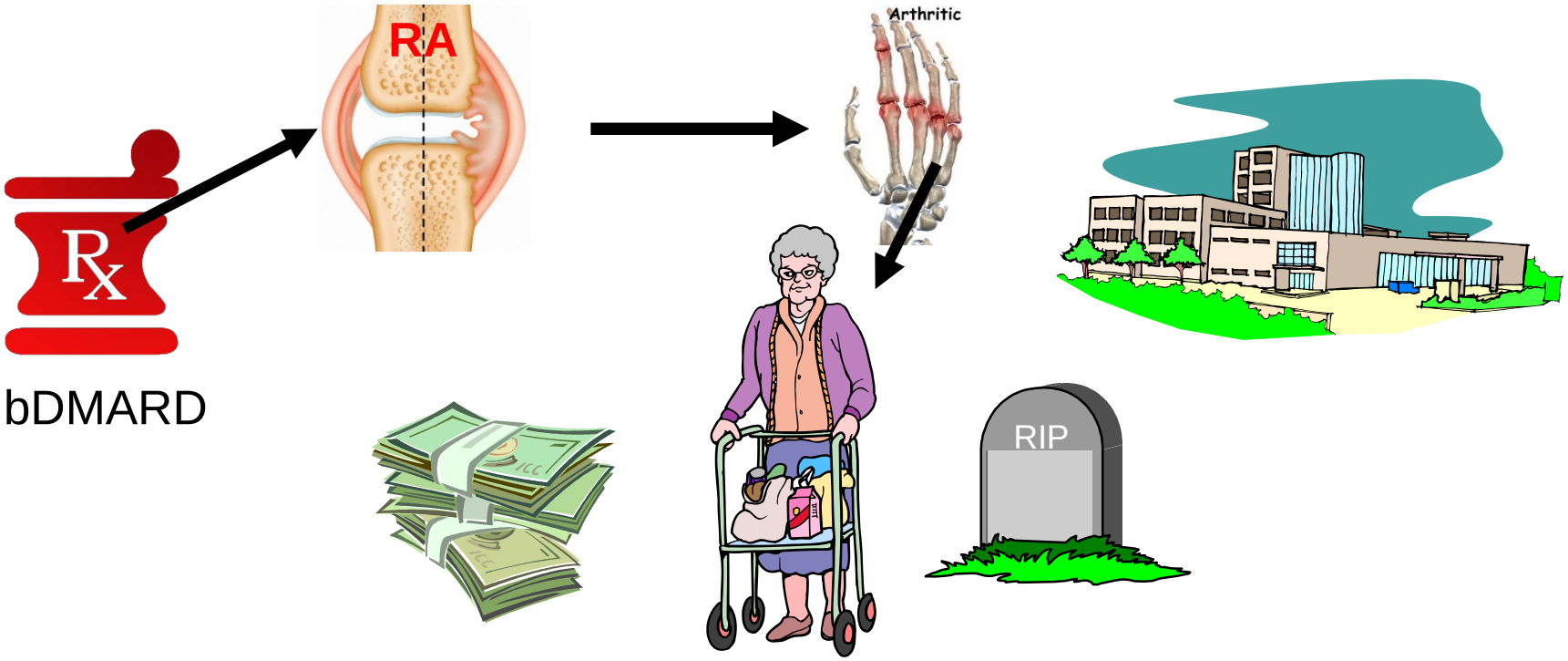
Leveraging novel simulation techniques to incorporate pharmacometrics in pharmacoeconomic models

J. Jaime Caro MDCM FRCPC FACP
ASCPT Annual Meeting 2018
Orlando, FL

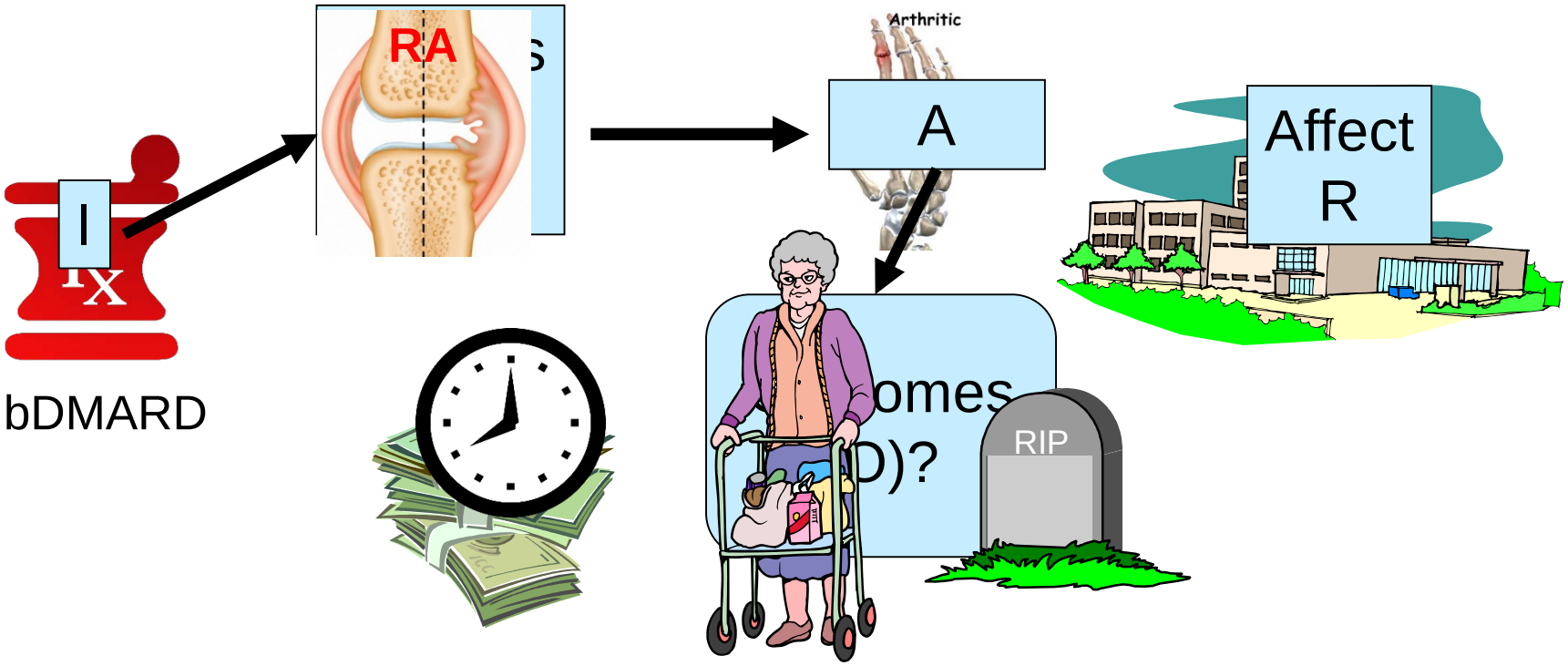
March 21, 2018

Typical PE Problem



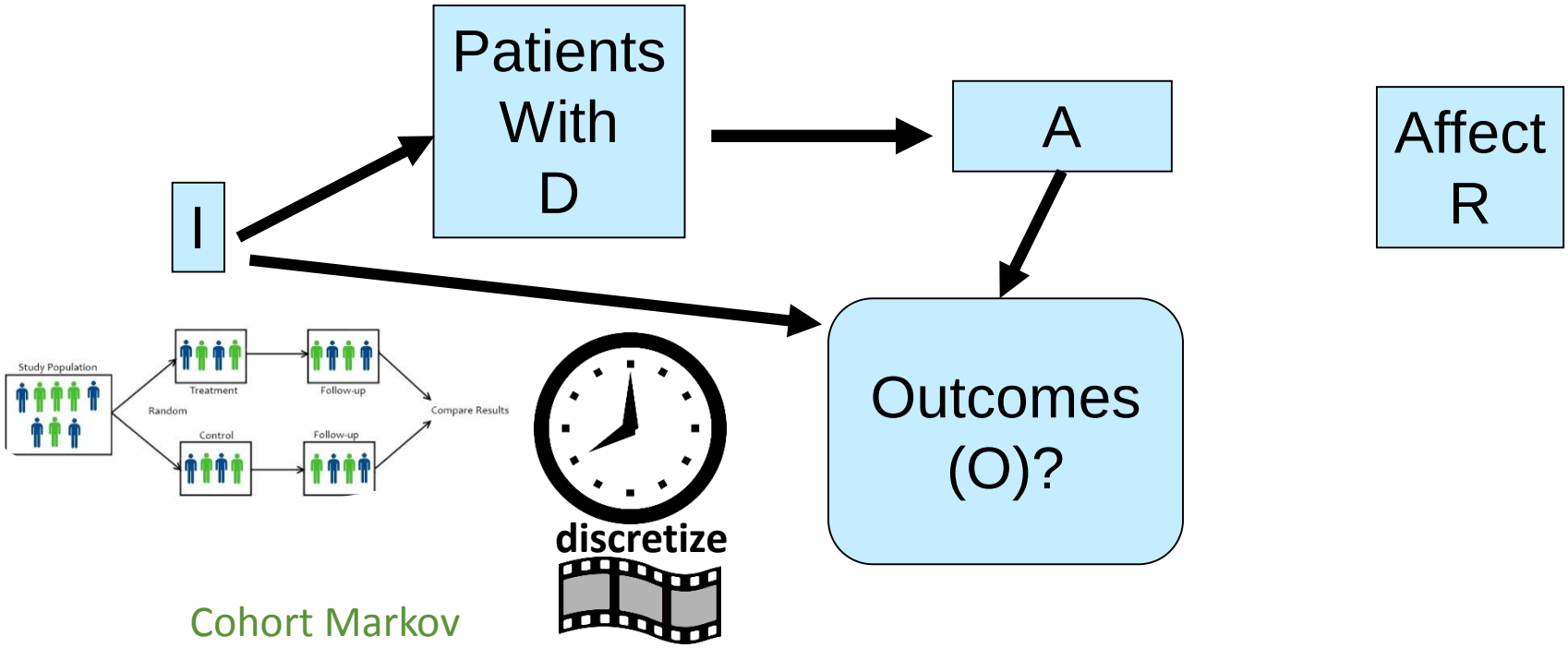
How much does Intervention (I) change some Aspect (A) of Disease (D) to improve Outcomes (O) & affect Resource (R) use over Time (T)?

Typical PE Problem

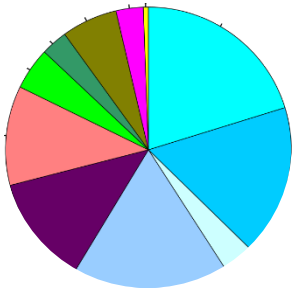


How much does Intervention (I) change some Aspect (A) of Disease (D) to improve Outcomes (O) & affect Resource (R) use over Time (T)?

PE Models



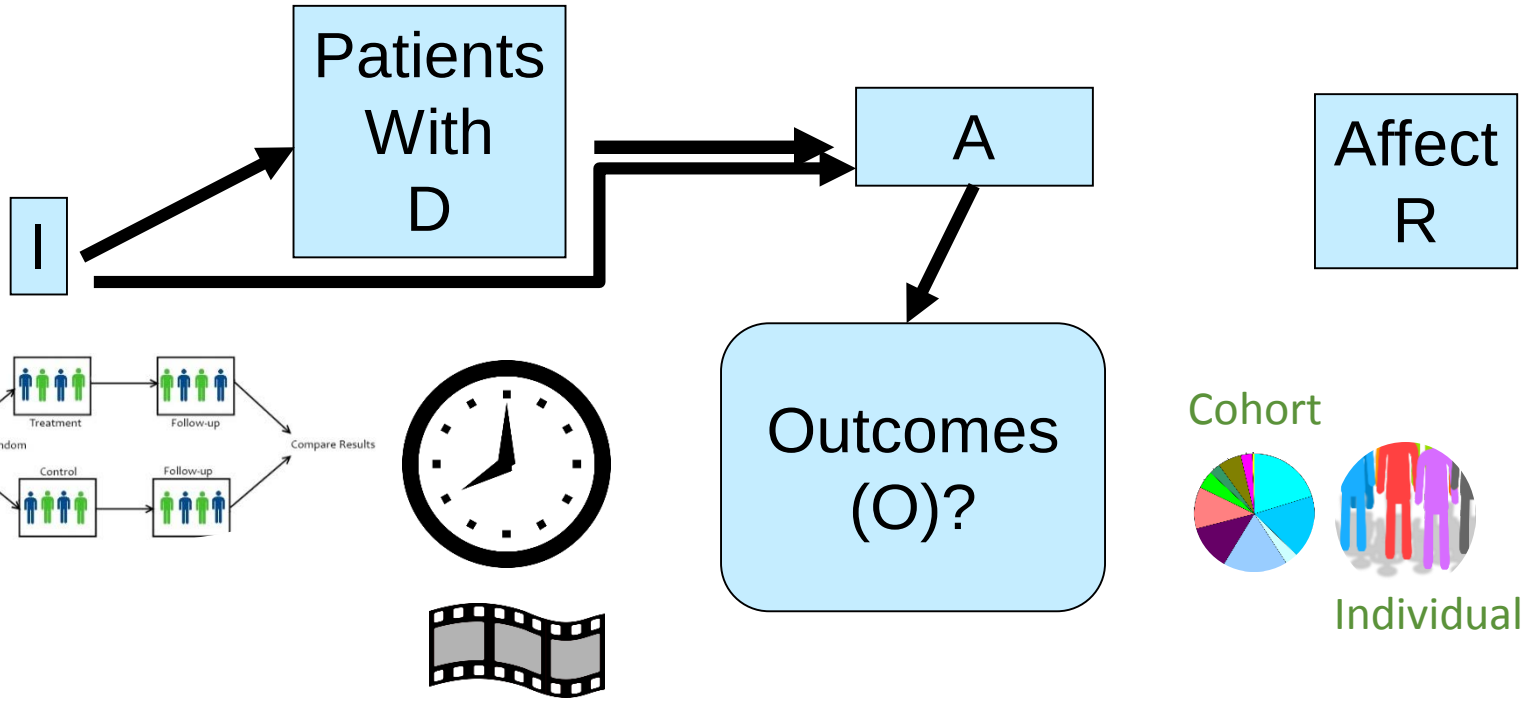
Cohort Markov

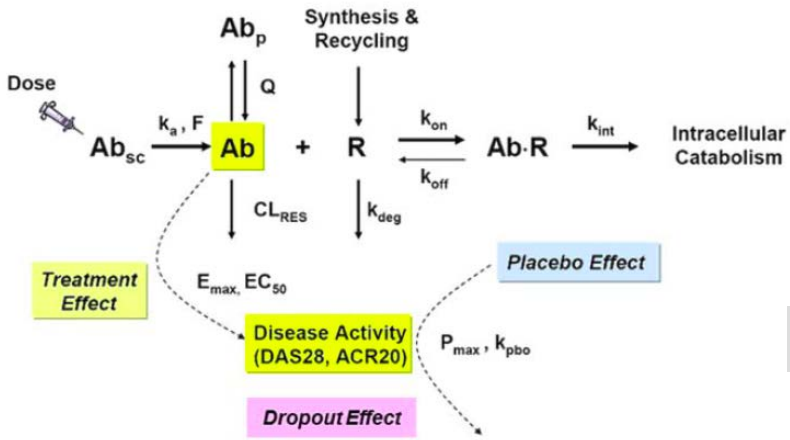


Individual

How much does Intervention (I) change some Aspect (A) of Disease (D) to improve Outcomes (O) & affect Resource (R) use over Time (T)?

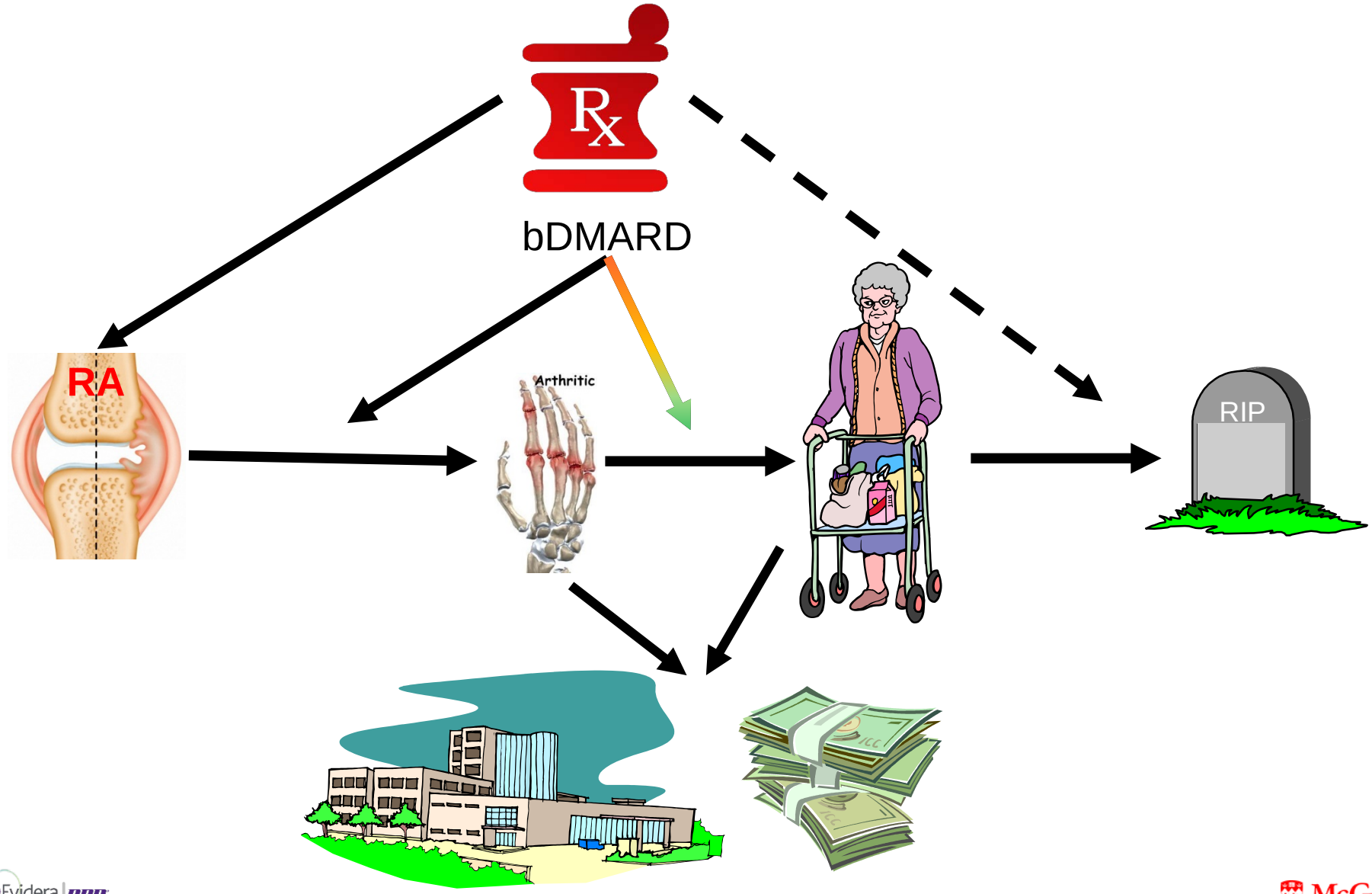
PKPD Models



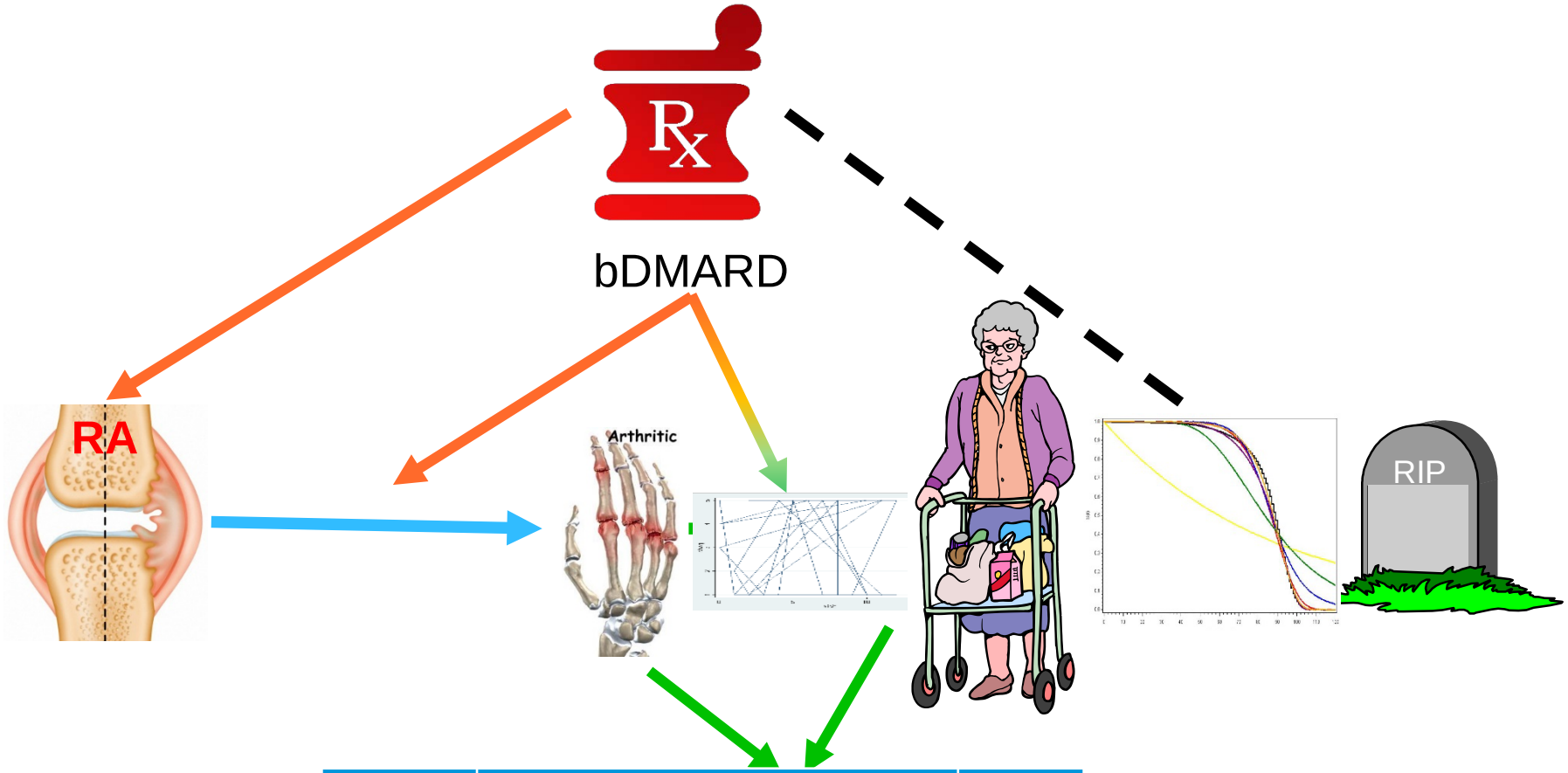


How much does Intervention (I) change some Aspect (A) of Disease (D) to improve Outcomes (O) & affect Resource (R) use over Time (T)?

Typical Problem



Typical Problem



Input	Description	cost
iCostRad	Cost of imaging at a visit	101
iCostLab	Cost of laboratory tests at a visit	84.78
iCostLabI	Extra cost of tests needed at 1st	122
iCostGP	Fee for a visit to GP	23
iCostRH	Fee for a visit to rheumatologist	28.27
iCostMTX	Cost per mg of methotrexate	.03

What is needed?

- Model concept that is natural
  - Accords closely with reality
  - Handles time accurately
- Very flexible
- Fast to create, easy to modify with new data or assumptions
- Able to examine the influence of assumptions (“structural” sensitivity analysis)
- Straightforward to review
- Simple to communicate
- Standard framework (easy to learn)
- Transparent, acceptable to stakeholders
- Preferably no need for additional software.

DICE simulation

What is DICE?

A modeling technique that conceptualizes the decision-analytic problem in terms of two fundamental aspects:

Conditions

- **Aspects that persist over time**
- **Interested in time spent at a given level (value)**
- **Many conditions can be present at once**
- **Have levels, which can change & affect events**

discrete integration

Events

- **Aspects that happen at a point in time**
- **Interested in number that happen (and when)**
- **Many can happen, at any time**
- **Can affect the level of a condition or other events**

The essentials of DICE

- **List of conditions**
  - Name (unique)
  - Level (at a given point in time)
- **List of events**
  - Name (unique)
  - Time of occurrence
- **Consequences of each event**
  - For itself (recurrence?)
  - For other events
  - For conditions

Specific to This model

- **Discrete-integrator**
  - Read conditions list
  - Read event list
  - Process event consequences in sequence
  - End simulation & report results.

General for All models

DICE View of Problem

- **List of conditions**
  - Name (unique)
  - Level (at a given point in time)
- **List of events**
  - Name (unique)
  - Time of occurrence
- **Consequences of each event**
  - For itself (recurrence?)
  - For other events
  - For conditions

- **Discrete-integrator**
  - Read conditions list
  - Read event list
  - Process event consequences in sequence
  - End simulation & report results.

1. List of conditions

Conditions

Name	Level
Activity	Lo

2. List of events

Events

Name	Time To Event
Start	Now
Respond	$Formula_{Rx1}$
Relapse	$Formula_{Rx1}$

3. Consequences of each event

Type	Name	Expression
Condition	Activity	Hi
Event	Respond	Ln(1-rand())/-hazard
Output	QALYs	0
Output	Costs	0

Start

Start
set Activity = hi
estimate time to Response

Response
set Activity = Lo
estimate time to Relapse
Accrue QALYs
Add up costs

Relapse
…

Implementation - software

- **List of conditions**
  - Name (unique)
  - Level (at a given point in time)
- **List of events**
  - Name (unique)
  - Time of occurrence
- **Consequences of each event**
  - For itself (recurrence?)
  - For other events
  - For conditions

Specific to This model

- **Discrete-integrator**
  - Read conditions list
  - Read event list
  - Process event consequences in sequence
  - End simulation & report results.

General for All models

Software

DICE Excel® Implementation

1. **List of conditions**
   - Vital status
   - Treatment
2. **List of events**
   - Death
   - Start

Conditions

Name	Level
Activity	
QALYs	
Cost	

Events

Name	Time To Event
Start	Now
Respond	Never
Relapse	Never

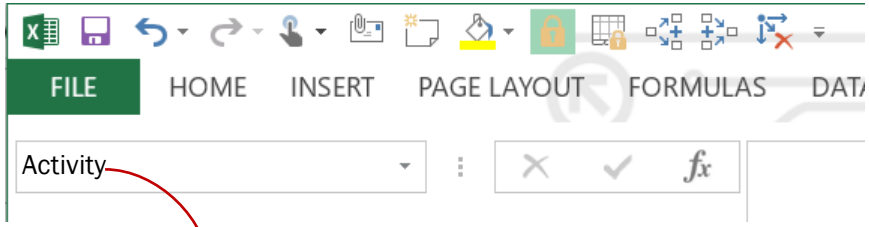
Start

Type	Name	Expression
Condition	Activity	Hi
Event	Respond	Ln(1-rand())/-hazard
Output	QALYs	0
Output	Costs	0

Getting the expressions to do something

Start

Type	Name	Expression
Event	Start	= Never
Condition	Activity	= Hi
Event	Respond	= Ln(1-rand())/-hazard
Output	QALYs	= 0
Output	Costs	= 0



Events

Name	Time To Event
Start	Now
Respond	Never

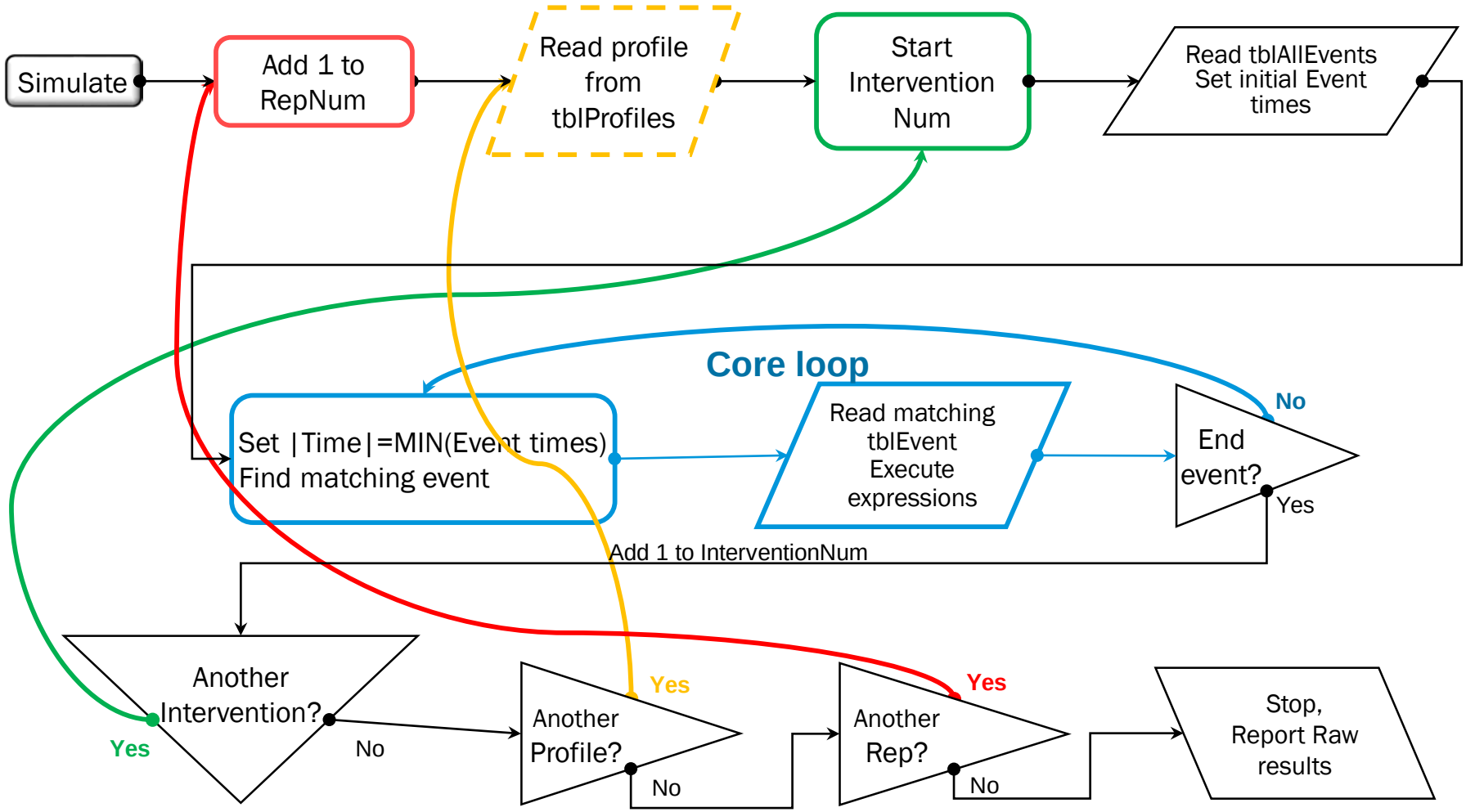
3.7

```
Do                                          'Loop through all events until E
    ThisEventName = UCase(EventTypes(rgeNextEvent, 4))
    ThisEvent = shEvents.ListObjects(ThisEventName).DataBodyRange.Value2
    For i = 1 To UBound(ThisEvent, 1)
        If ThisEvent(i, 3) <> "" Then
            rgeCalcCell = "=" & ThisEvent(i, 3)
            Range(ThisEvent(i, 2)) = rgeCalcCell.Value
            shEvents.Calculate
        End If
    Next i
    rgeCalcCell = ""                        'Housekeeping of cell used for ca
Loop Until ThisEventName = "TBLEND"         'If End-event
```

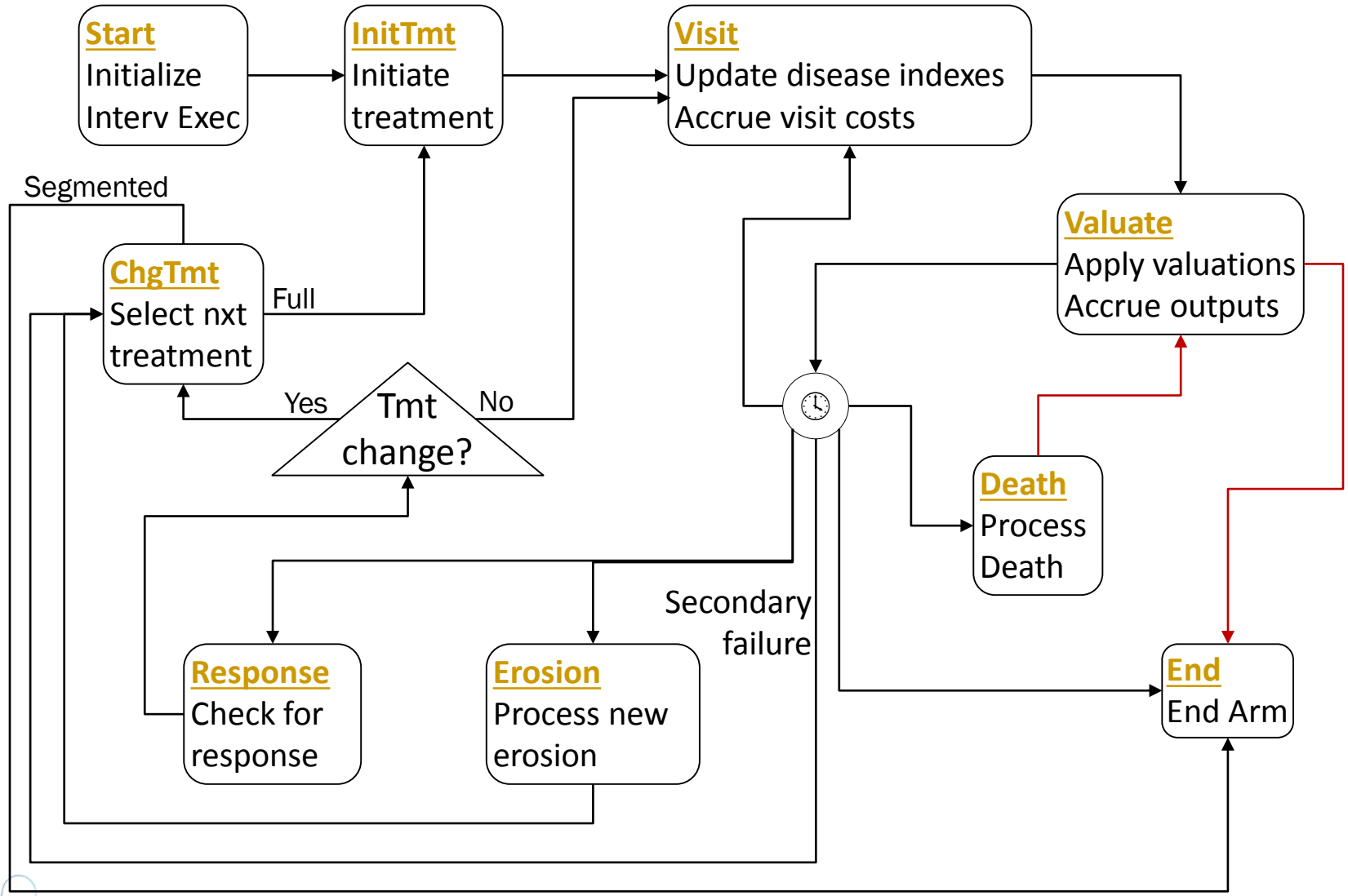
Conditions

Name	Level
Activity	Hi
QALYs	0
Cost	0

DICE loops

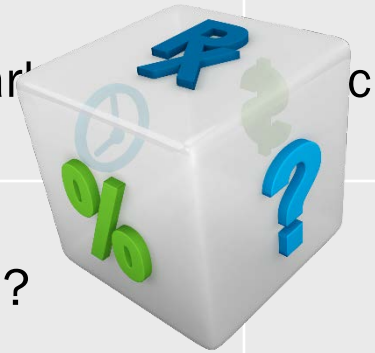

Simulate
Add 1 to RepNum
Read profile from tblProfiles
Start Intervention Num
Read tblAllEvents Set initial Event times
Core loop
Set |Time|=MIN(Event times)
Find matching event
Read matching tblEvent Execute expressions
End event?
No
Yes
Add 1 to InterventionNum
Another Intervention?
Yes
No
Another Profile?
Yes
No
Another Rep?
Yes
No
Stop, Report Raw results

DICE Path Diagram

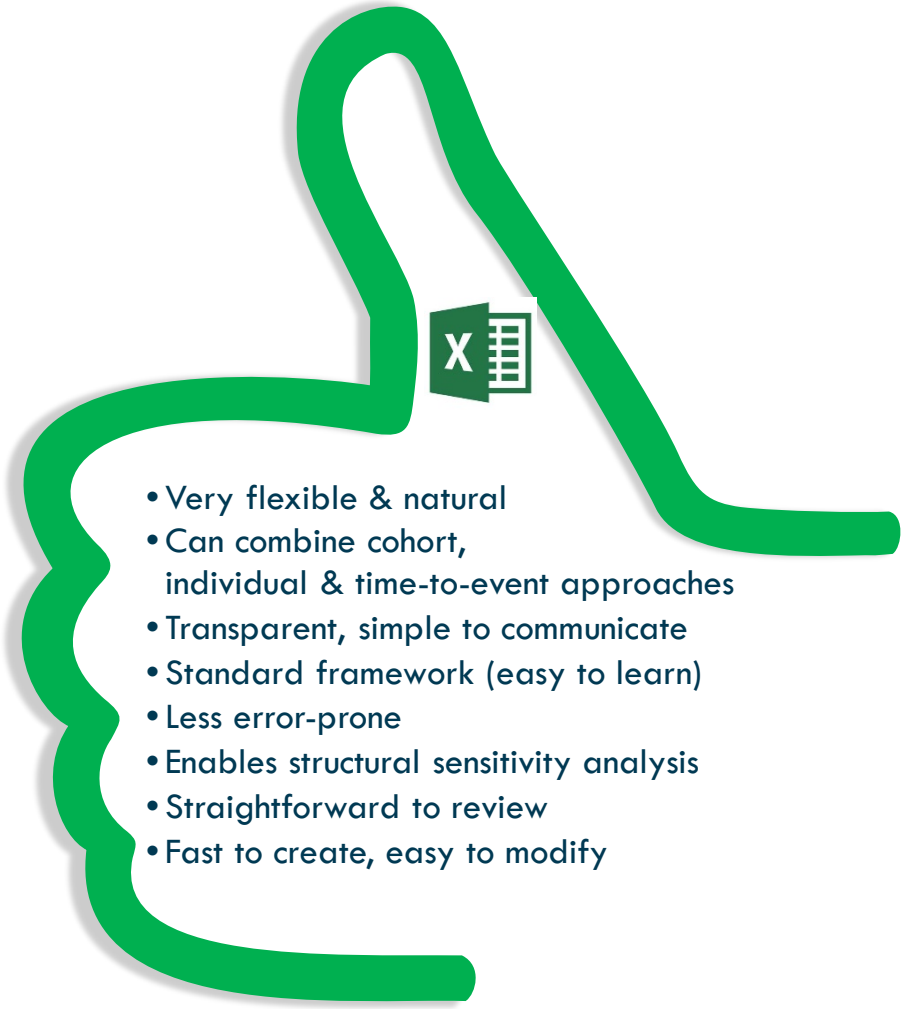


Modeling

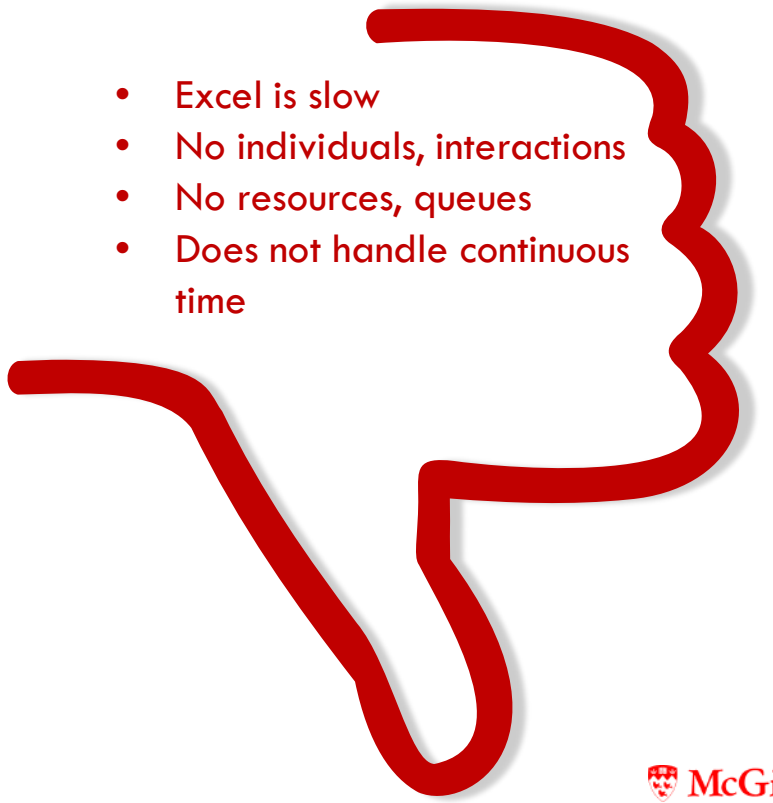
	Deterministic	Stochastic
Periodic check	Mar	crosimulation
Time-to-event	?	"DES"



Segmented Approach Using DICE: Advantages & limitations



- Very flexible & natural
- Can combine cohort, individual & time-to-event approaches
- Transparent, simple to communicate
- Standard framework (easy to learn)
- Less error-prone
- Enables structural sensitivity analysis
- Straightforward to review
- Fast to create, easy to modify



- Excel is slow
- No individuals, interactions
- No resources, queues
- Does not handle continuous time