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Direct Comparison of Apremilast and Best Supportive Care Using a Discrete Event Simulation

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**DIRECT COMPARISON OF
APREMILAST AND BEST
SUPPORTIVE CARE
USING A DISCRETE EVENT
SIMULATION**

Zoe Clancy, PharmD

OUTLINE

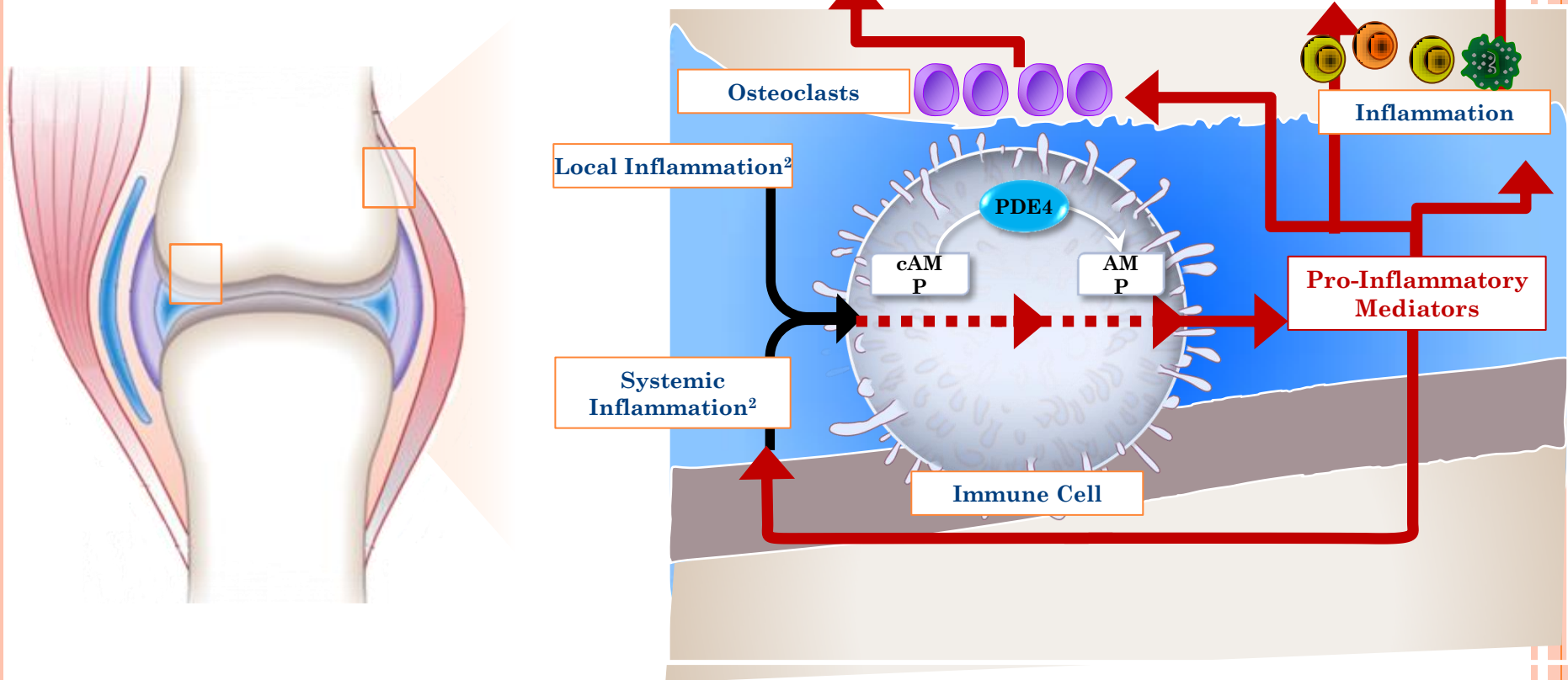
- Psoriatic Arthritis Disease Brief
 - Mechanism of action
 - Differences between Psoriatic Arthritis and Rheumatoid Arthritis
 - Current treatment
- Discrete Event Simulation
 - Definition
 - Model Overview
 - Model Results





PSORIATIC ARTHRITIS DISEASE BRIEF

PSA IS A CHRONIC INFLAMMATORY DISEASE OF THE JOINTS AND SKIN RESULTING FROM AN UNCONTROLLED IMMUNE RESPONSE¹



Over-production of TNF- α as well as other cytokines, alters bone homeostasis, resulting in the joint damage seen in PsA⁴

1. Schafer. *Biochem Pharmacol.* 2012;83:1583
2. Serezani et al. *Am J Respir Cell Mol Biol.* 2008;39:127
3. Gottlieb et al. *J Am Acad Dermatol.* 2008;58:851
4. Mensah et al. *Curr Rheumatol Rep.* 2008;10(4):311

PSA DIFFERS FROM RHEUMATOID ARTHRITIS (RA) BASED ON THE PRESENCE OF PSORIATIC-ASSOCIATED CONDITIONS AND THE DISTRIBUTION AND APPEARANCE OF THE AFFECTED JOINTS

Clinical Feature	PsA	RA
Psoriatic skin lesions present	Common	No
Psoriasis-associated nail symptoms	Common	No
Distribution of affected joints	Often asymmetrical Various joints affected	Symmetrical Primarily involving hands and wrists
Appearance of the affected joint	More generalized swelling Produce a sausage-like appearance in fingers or toes	Pronounced swelling over joints (RA nodules)
Disease progression	Variable	Predictable
Rheumatoid factor status	Seronegative	Seropositive



KEY CONCEPTS

- In 75% of cases, psoriasis precedes the joint disease.
- In 15% of cases, the onset of skin disease is at the same time as onset of joint involvement.
- In 10% of cases, the joint disease precedes the psoriasis.



PSA AND QOL

- For people with psoriatic arthritis, quality of life is impacted by both the physical symptoms of the disease and the emotional burden of sometimes disfiguring skin symptoms.
- Compared to rheumatoid arthritis and ankylosing spondylitis, people with psoriatic arthritis report more psychosocial problems.
- This finding fits with data from a survey of people with psoriasis, which found that 75 percent of patients believe the skin condition had a moderate to large negative impact on their quality of life, with alteration in their activities and work.



PSA HAS A SIGNIFICANT NEGATIVE IMPACT ON HEALTH-RELATED QUALITY OF LIFE (HRQoL)

- Decreased QoL as measured by the Medical Outcomes Short-Form 36 Questionnaire (SF-36) scores in patients with PsA compared to the general population:¹
- 19% of patients with PsA claimed their disease resulted in “marked physical limitations”²
- 8.2% of patients sought assistance for home activities from friends or family³
- Both physical functioning and emotional well-being are decreased.
- In patients with PsA and psoriasis:
 - Arthritis component - greater impact on physical functioning
 - Psoriasis component - greater impact on emotional well-being
 - Skin lesions associated with poor self-image and distress from pruritus and pain.

⁸Husted JA, et al. *J Rheumatol*. 1997 Mar;24(3):511-7.

⁹Torre Alonso JC, et al. *Br J Rheumatol*. 1991 Aug;30(4):245-50.

¹⁰Kimball AB, et al. *J Drugs Dermatol*. 2007 Mar;6(3):299-306.



EPIDEMIOLOGY

Prevalence 5% - 40% of people with psoriasis

Race Affects Caucasians more than other races

Gender Men and women equally affected

Age of onset 40–50 years of age, can occur earlier



TREATMENT OPTIONS

Mild Disease

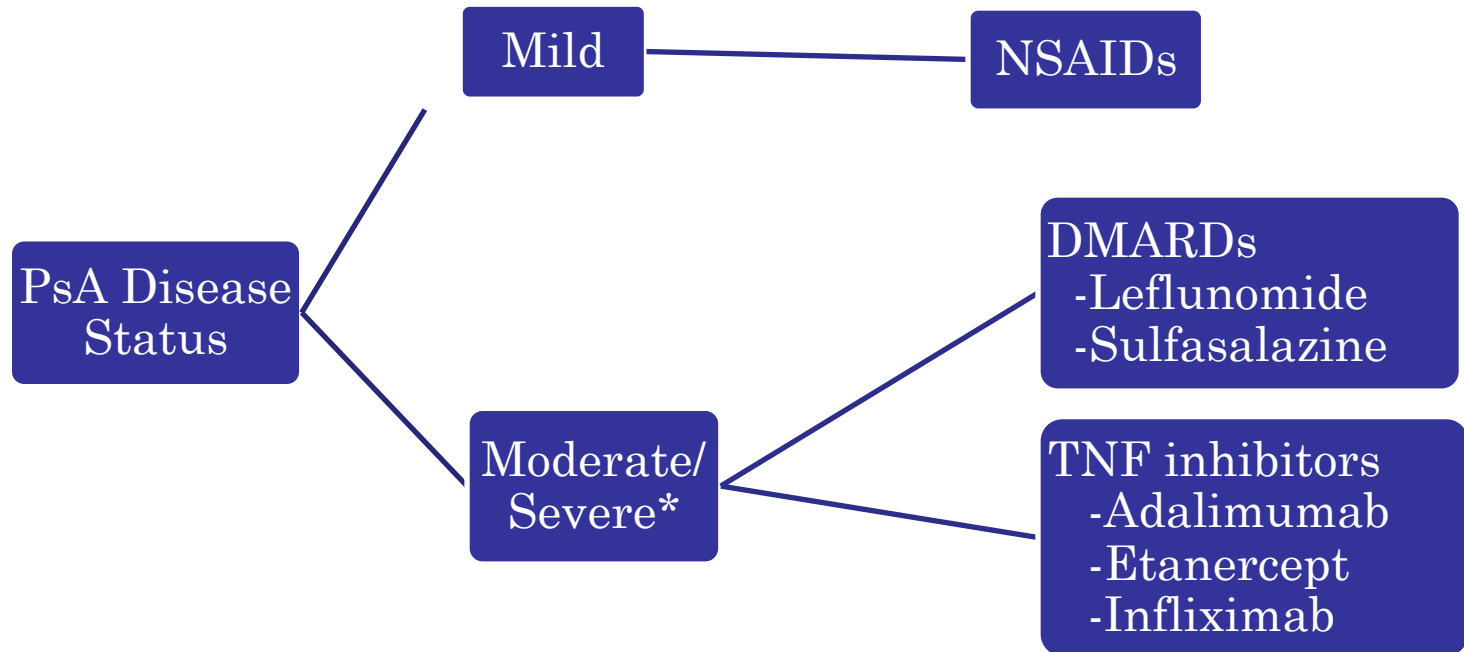
- NSAIDs

Moderate to Severe Disease

- Corticosteroids
- Traditional DMARDs
 - MTX
 - Sulfasalazine
 - Leflunomide
- Biologic DMARDs



National Guideline Recommendations in Patients with PsA



*No evidence supporting DMARDs ahead of TNF inhibitors (effect size: TNF inhibitors > traditional DMARDs). However, TNF inhibitors are recommended for patients who fail to respond to at least one DMARD therapy unless poor prognosis present.

Grade A=Based on evidence from meta-analysis of randomized controlled trials (RCT) or ≥ 1 RCT



Adverse Effects Limit the Benefits of Therapy with Traditional Systemic DMARDs and Biologics

■ Traditional systemic agents

- Methotrexate (MTX) has weak and conflicting evidence in the management of PsA with risks of serious toxic reactions.
- MTX is not approved by the FDA
- Leflunomide does not have FDA approval and requires monitoring for hepatic toxicity
- Sulfasalazine has limited evidence in the management of PsA with rarely occurring serious toxicities.

■ Biologics

- Mild injection-site/infusion reactions
- Black box warning of risk of serious infections and malignancies
 - Increased risk of infection
 - Overall infections, odds ratio 1.18 (95% confidence interval, 1.05-1.33)²
 - Patients with PsA are at greater risk for mortality from infection.



The Significant Burden Associated with PsA

■ **Patients with PsA:**

- Suffer from limited mobility, pain, inflammation and stiffness as well as skin lesions from psoriasis
- Have a poorer quality of life
- Are less likely to be employed and less likely to be productive
- Incur higher healthcare costs

■ **New PsA therapies are needed that demonstrate:**

- Effective Treatment in Patients with Active Psoriatic Arthritis
- Improved Safety and Better Tolerability than Traditional DMARDS and Biologics
- Patient Convenience over Injectable Biologics
- Cost savings compared to Biologics



APREMILAST

- Apremilast is a first-in-class PDE4 inhibitor
 - MOA: modulates pro-inflammatory and anti-inflammatory mediators
 - Administration: oral and does not need dose adjustments
- This drug represents a novel treatment option for patients and can represent a delay in biologic therapy¹⁴

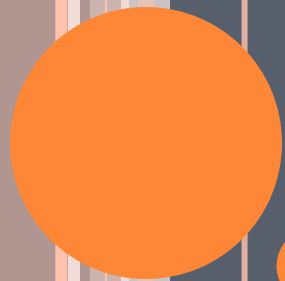
14. Tencer T, et al. (2014) Economic evaluation of sequencing strategies in the treatment of psoriatic arthritis in the United States (abstract). Value in Health (17)3: A46.



OUTCOME MEASURES OF PSA

- ACR response criteria: 20%, 50%, 70% (validated in RA, not PsA)
 - Tender and swollen joint count (modified for PsA to include DIP and CMC joints: 78/76, 68/66)
 - 3/5: patient global, physician global, patient pain, HAQ, acute phase reactant (sed rate, CRP)
- Psoriatic Arthritis Response Criteria (PsARC)
 - Improvement in at least 2 of 4 criteria, including:
 - Physician global assessment (0–5)
 - Patient global assessment (0–5)
 - Tender joint score ($\geq 30\%$)
 - Swollen joint score ($\geq 30\%$)
 - Improvement in at least 1 of 2 joint scores
 - No worsening in any criteria





DISCRETE EVENT SIMULATION

All Models Are Wrong, But
Some Are Useful

-George E.P. Box



DISCRETE EVENT SIMULATION (DES)

- DES is a modeling technique that is event-based

Advantages vs Markov Models

- DES can incorporate new data as it becomes available
- Can use an individual patient's values and examine the decision from his or her point of view
- Can capture multiple events with competing risks



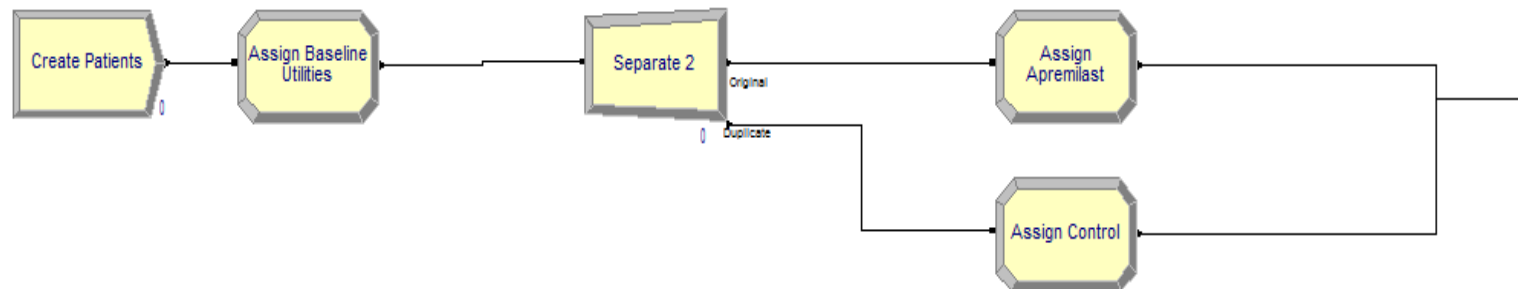
BASIC MODEL STRUCTURE

- Patients with active psoriatic arthritis who have failed methotrexate (MTX) therapy will be split into two groups: apremilast followed by best supportive care (BSC) and patients only receiving BSC



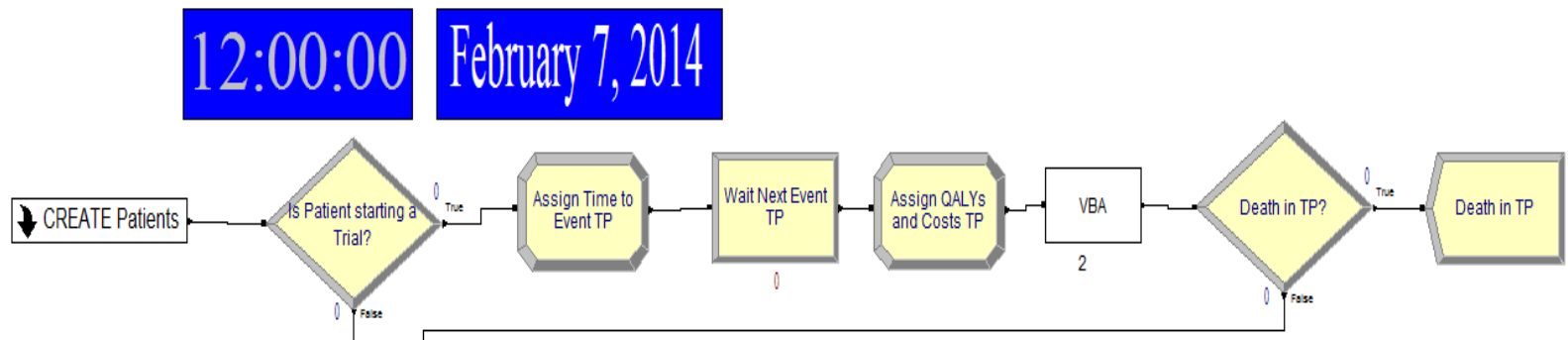
STEP 1: CREATE PATIENTS AND ASSIGN CHARACTERISTICS

- Assign Baseline Utilities:
 - Age
 - Gender (45% male)
 - Life expectancy
 - Mortality



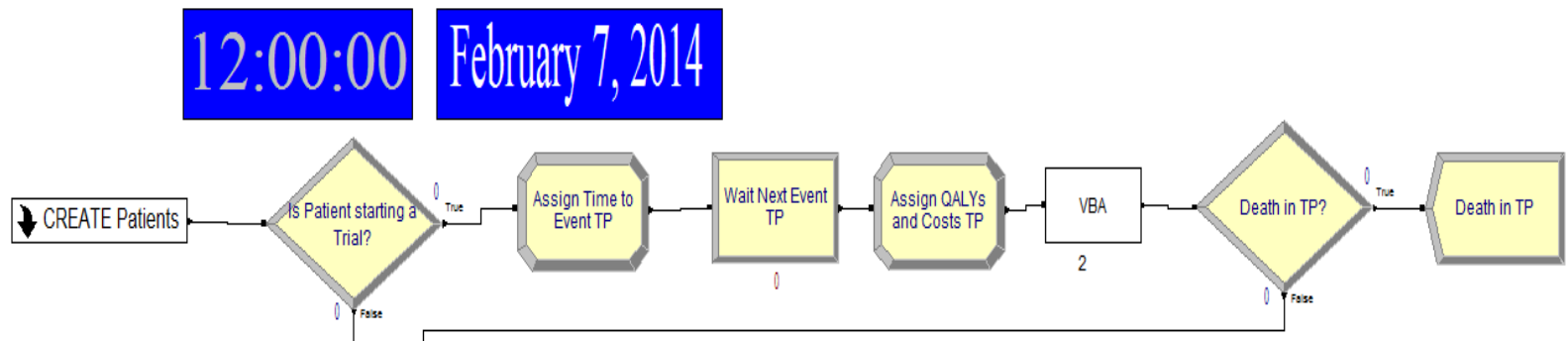
STEP 2: PATIENTS ENTER EITHER APR OR BSC TREATMENT ARM

- If ‘Is Patient starting a Trial?’ is TRUE, then patients enter APR arm
- ‘Assign Time to Event TP’ sets the next event to death and logs the time at the beginning of the time-to-event period
- Time advances in “Wait Next Event TP”



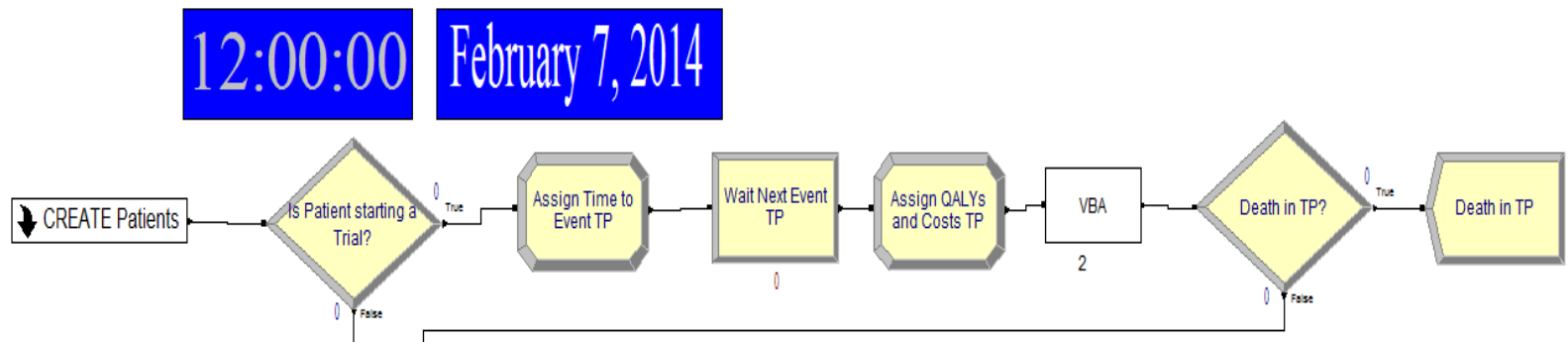
STEP 2: PATIENTS ENTER EITHER APR OR BSC TREATMENT ARM

- Patients move to ‘Assign QALYs and Costs TP’ where QALYs and Costs are calculated
- The VBA module is used to calculate Other Healthcare Costs
 - The VBA module computes the patient’s age each month and tallies the costs over the course of the period



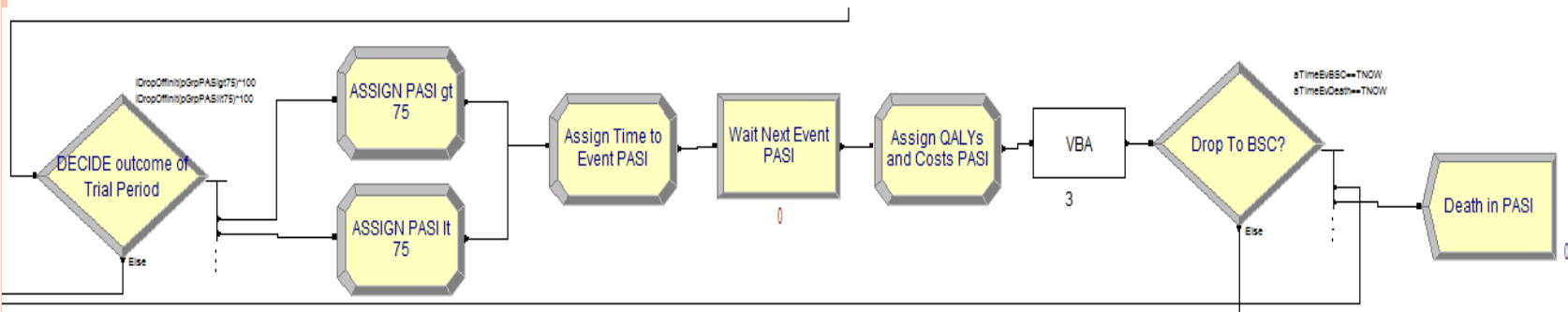
STEP 2: PATIENTS ENTER EITHER APR OR BSC TREATMENT ARM

- After costs and QALYs have been assigned, ‘Death in TP?’ checks to see if the time of death event was prior to the end of the Trial Period
- If so, patient is disposed of in the model, otherwise patient continues to BSC



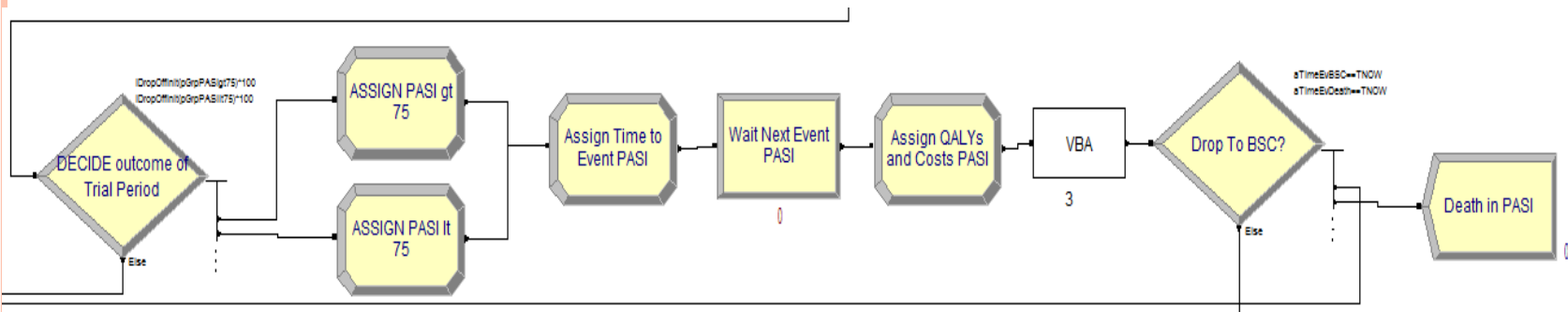
STEP 3: DECIDE IF TREATMENT WAS EFFECTIVE (OR NOT)

- Patients enter a decision module ('DECIDE outcome of Trial Period') which decides whether the patients achieved a PsARC score (effective treatment) or not
- If treatment effective, patients are assigned to a PASI group to allocate future costs and QALYs
- Patients who are not successfully treated move to the BSC arm



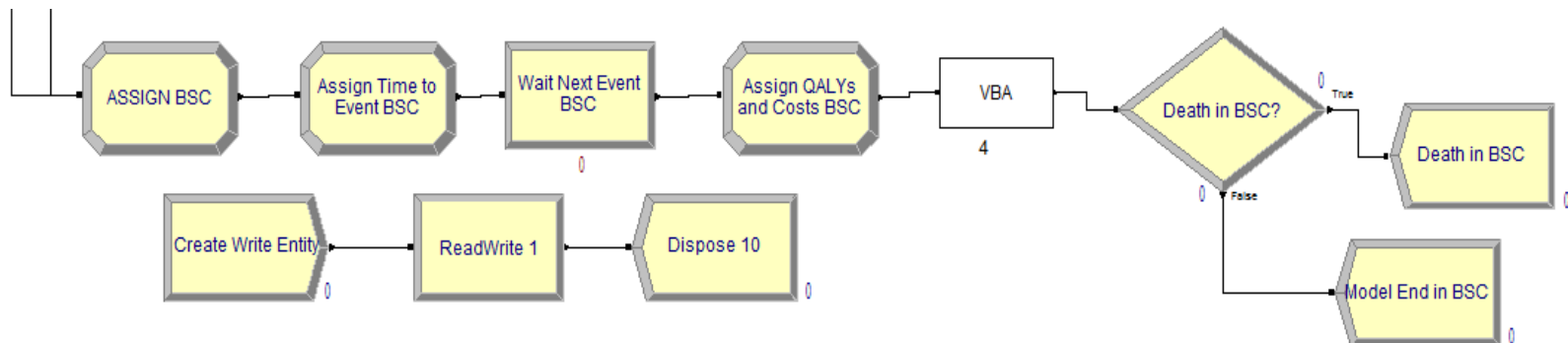
STEP 3: DECIDE IF TREATMENT WAS EFFECTIVE (OR NOT)

- ‘Assign Time to Event PASI’ module assigns a length of time until patients move to BSC
- Similar to the Trial Period arm, patient is advanced in time through the ‘Wait Next Event PASI’ module to the sooner of either Death or BSC or model end
- Costs and QALYs are assigned as in Trial Period arm



STEP 4: BSC, DEATH, OR MODEL END

- Patients enter BSC arm either at beginning of the model run or through discontinuation of treatment
- Similar to Trial Period and Apremilast Arm, with patients disposed of at the end
- The Excel read/write modules are also shown



MODEL ASSUMPTIONS

- Patients who enter the BSC arm do not go back to apremilast therapy
- There are no changes to BSC or treatment paradigms of PsA in clinical practice over the time horizon of the model (5 years)
- The population to which the model is applied to follows the age and life expectancy of that in the model
- HAQ scores return to baseline after discontinuation of treatment
- No monitoring or lab costs for apremilast



MODEL LIMITATIONS

- Data was sourced from clinical trials and not real world
- PASI is used as the trial period endpoint, but is not the clinical trial endpoint for efficacy
- Indirect costs of treatment are not accounted for in the model



MODEL RESULTS

Rep	Control		Apremilast		
	Costs	QALYs	Costs	QALYs	
1.00	\$ 30,558.54	19.70	\$ 288,081.27	34.00	
2.00	\$ 107,698.74	53.81	\$ 162,649.05	54.36	
3.00	\$ 66,412.11	36.19	\$ 302,328.11	48.89	
4.00	\$ 139,131.43	68.18	\$ 651,137.37	74.52	
5.00	\$ 32,584.15	17.74	\$ 128,977.00	20.67	
6.00	\$ 86,104.37	45.88	\$ 188,795.84	47.13	
7.00	\$ 75,148.61	38.87	\$ 242,798.90	40.83	
8.00	\$ 94,376.35	50.68	\$ 198,235.75	53.69	
9.00	\$ 99,138.22	53.90	\$ 224,178.43	60.20	
10.00	\$ 96,838.01	57.71	\$ 226,460.36	59.30	
11.00	\$ 75,393.11	41.54	\$ 210,705.91	48.16	
12.00	\$ 106,148.80	55.74	\$ 504,847.20	60.29	
13.00	\$ 103,474.64	50.81	\$ 123,192.79	51.13	
14.00	\$ 73,509.76	37.78	\$ 142,757.01	38.63	
15.00	\$ 113,050.81	64.10	\$ 246,031.07	65.72	
	Total	\$ 1,299,567.67	692.65	\$ 3,841,176.07	757.51
	Avg/Patient	\$ 17,327.57	9.24	\$ 51,215.68	10.10
			AVG	\$ 33,888.11	0.86

Comparison of DES to Markov Model

- Model cost results are within 20%

	QALY/ patient	Cost/ patient
Markov Model	0.29	\$41,338
DES	0.86	\$33,888



CONCLUSIONS

- DES models are more adaptable, compared to Markov models
 - Once data becomes available, for example QOL instrument data, the DES is easily updated
- DES and Markov models share limitations, specifically the availability and quality of data
 - Markov models have less data requirements
- A comparison of two models with the same data shows differences that can be attributed to
 - time to event that was used to calculate drop off to BSC
 - distributions used for age and life expectancy



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