Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value

Public Meeting – March 24, 2017

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

WIRELESS INTERNET: HMS Guest

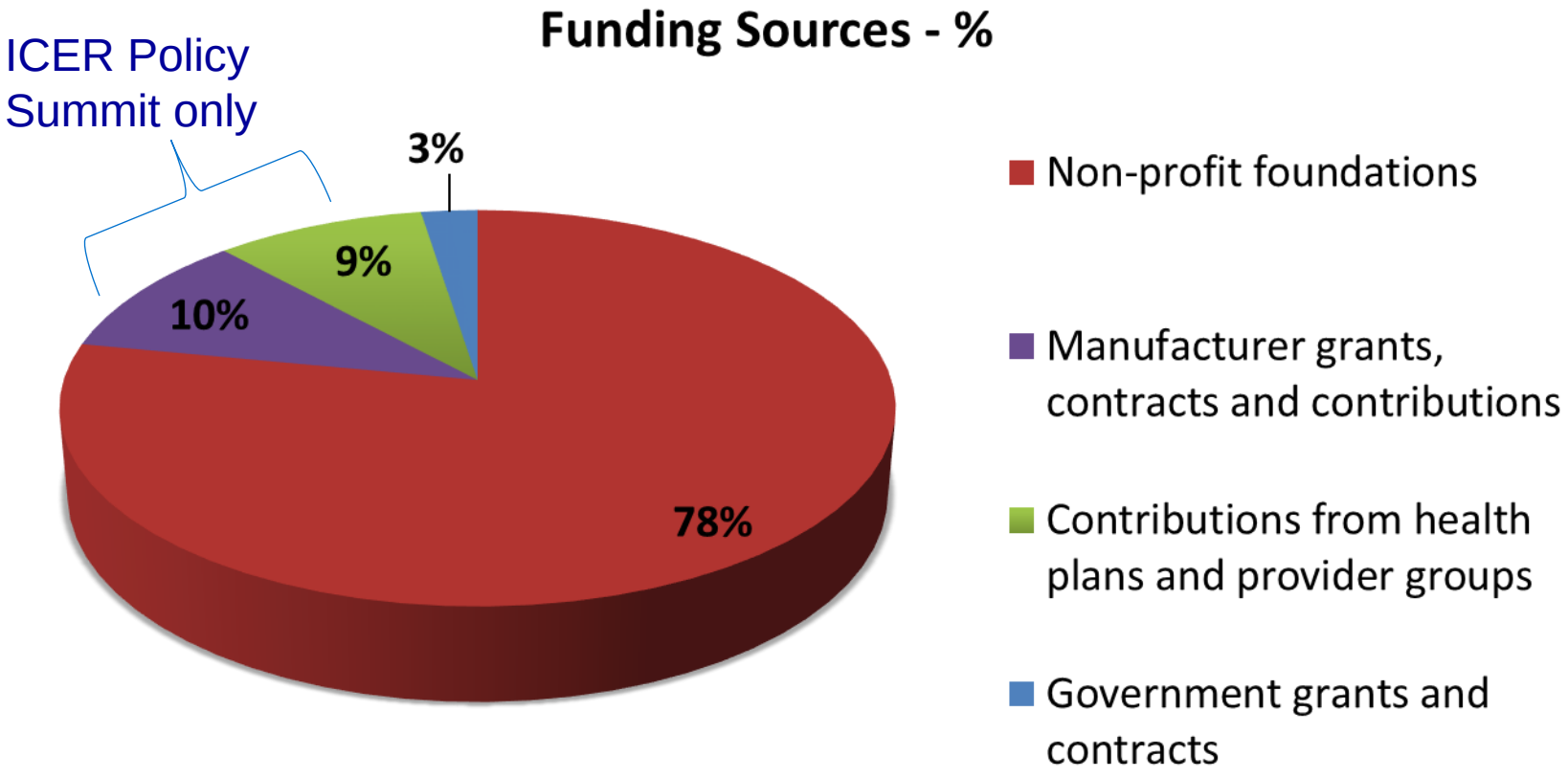
Welcome and Introduction

- New England Comparative Effectiveness Public Advisory Council (CEPAC)

- The Institute for Clinical and Economic Review (ICER)

Sources of Funding, 2017

ICER Policy Summit only



Welcome and Introduction

- Why are we here today?
  - Innovation bringing substantial benefits to patients, their families, communities, and society

    - "When our arthritis community began in 1999 our patient events were held in wheelchair-accessible locations with ample space for up to one-third of the participants and their wheelchairs or other assistive devices. Patients were overwhelmingly on cDMARD therapy such as Methotrexate. Biologics, not Methotrexate, took away the wheelchairs."

      -- Global Healthy Living public comments

Welcome and Introduction

- Why are we here today?
  - Difficulties accessing drugs
    - Step therapy protocols
    - Requirements to switch drugs with new insurance
    - High out-of-pocket costs for patients
  - Cost to the system, prices, and value

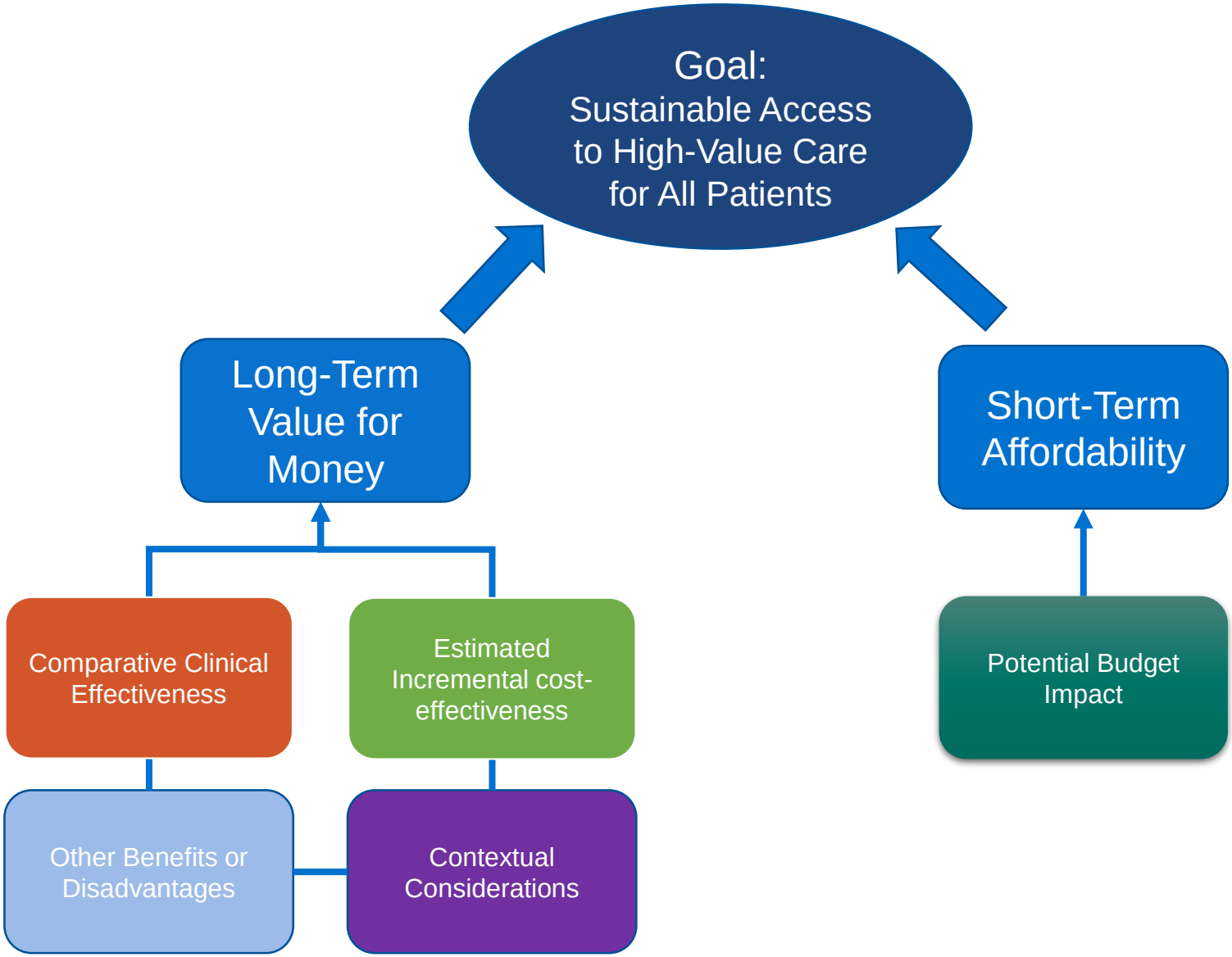
Drug net price inflation and value

Drug	Net price 2016	Price to meet $150K/QALY	Year at that price or lower
Rituximab	$710	$534	2009
Abatacept sc	$814	$540	2013
Tocilizumab sc	$719	$614	2015
Adalimumab	$1,554	$978	2013
Certolizumab peg	$1,288	$875	2013
Etanercept	$777	$504	2014
Golimumab sc	$2,905	$1,593	2012
Infliximab	$817	$598	2010

Welcome and Introduction

How was the ICER report on treatments for RA developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- University of Washington cost-effectiveness modeling
- Public comment and revision
- Clinical expert report reviewers
  - Andrew Concoff, MD
  - Max Hamburger, MD
  - Andrew Laster, MD
  - Kent Johnson, MD
  - Matthew Liang, MD, MPH
  - Elizabeth Tindall, MD
- Patient expert report reviewers
  - Arthritis Foundation: Sandie Preiss, MPA; Guy Eakin, PhD ; and Kayla Amodeo, PhD
  - Janet Stearns Wyatt, PhD, RN, FAANP
- How is the evidence report structured to support CEPAC voting and policy discussion?


Goal:
Sustainable Access to High-Value Care for All Patients
Long-Term Value for Money
Short-Term Affordability
Comparative Clinical Effectiveness
Estimated Incremental cost-effectiveness
Potential Budget Impact
Other Benefits or Disadvantages
Contextual Considerations

Agenda

9:30am: Welcome and Opening Remarks

9:45am: The Patient Experience: Accessing Care

The Arthritis Foundation

9:55am. Presentation of the Evidence

Evidence Review: Daniel A. Ollendorf, PhD, ICER

Comparative Value: Jonathan Campbell, PhD, University of Colorado School of Pharmacy

10:50am: Manufacturer Public Comments: Panel & Discussion

11:40pm: Public Comments and Discussion

12:15pm: Lunch

1:00pm: New England CEPAC Deliberation and Votes

2:00pm: Policy Roundtable

3:30pm: Reflections and Wrap Up

4:00pm: Meeting Adjourned

Arthritis Foundation Patient Data Presentation

Sandie J. Preiss
National VP Advocacy & Access
Arthritis Foundation

Arthritis Foundation℠

March 24, 2017

Surveys

The AF conducted **3 patient surveys** to help inform ICER of the patient experience

1. Rheumatoid Arthritis: Patient Treatment Experiences
2. Impact of Innovative Therapies on Rheumatoid Arthritis Patients
3. Utilization Management Survey

Limitations:

- Self reported data
- Not generalizable to other chronic diseases
- Cross-sectional design

Rheumatoid Arthritis: Patient Treatment Experiences

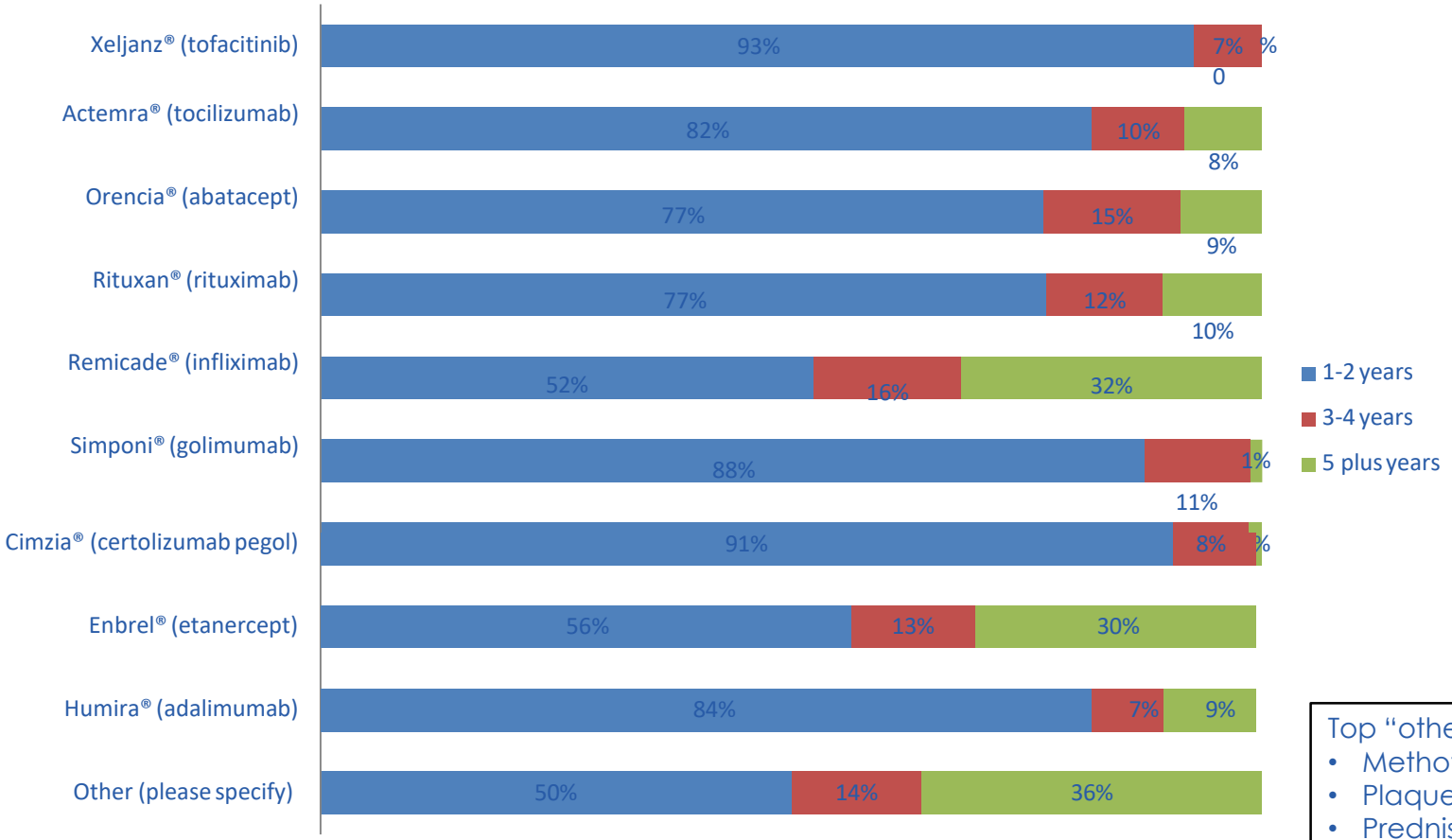
Survey 1

Arthritis Foundation℠

Methodology

- Delivery method: Online survey; Qualtrics software
- Population: Arthritis Foundation constituents with expressed interest in RA
- Dates open: November 3-16, 2016
- Total Responses: ***n*= 3,186**

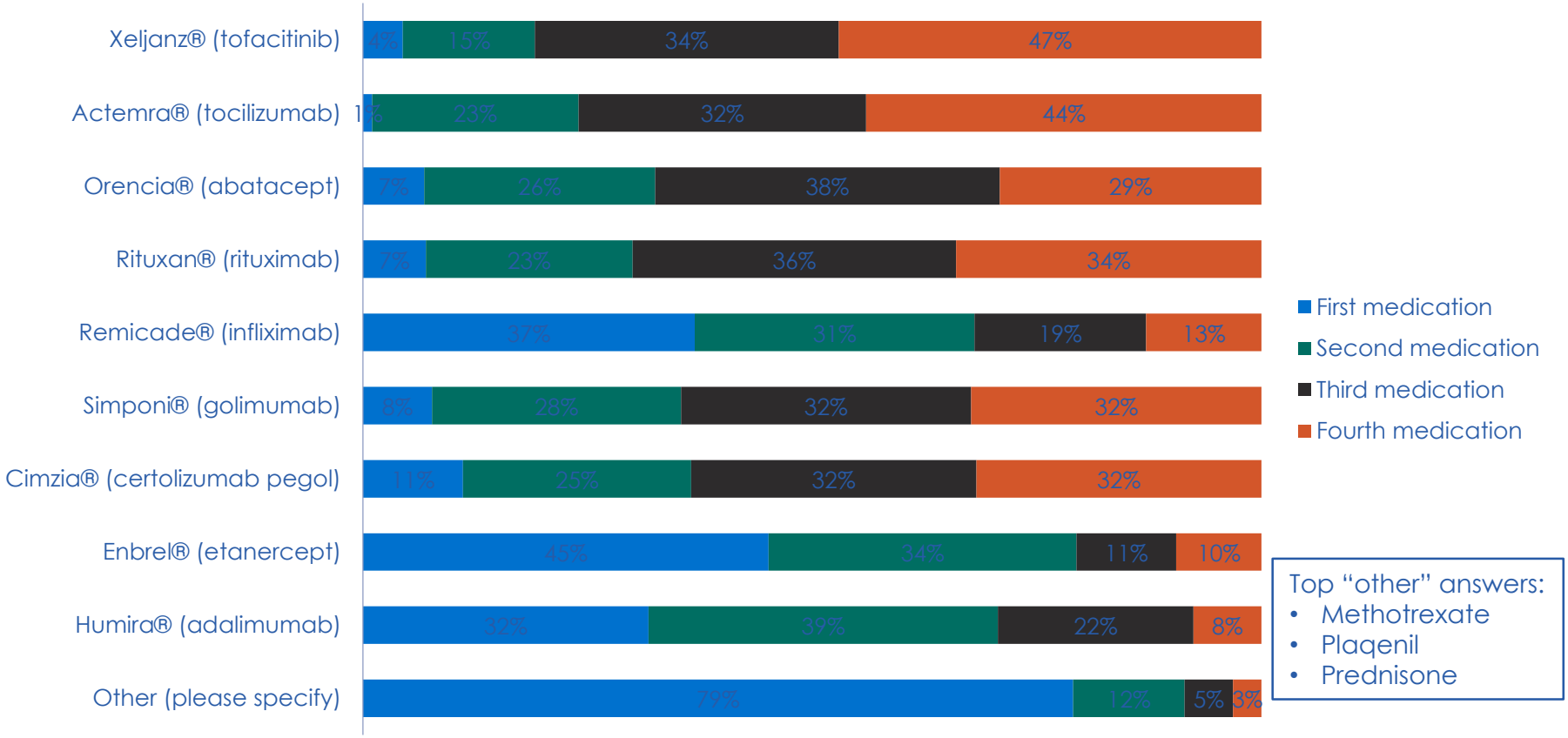
People with RA often had to change medications early in their course of treatment



Top "other" answers:
- Methotrexate
- Plaquenil
- Prednisone

Q - If applicable, how many MONTHS have you been on (or were you on) each medication? Mark all that apply. n=1,769

Most respondents have taken multiple medications over the course of their RA treatment

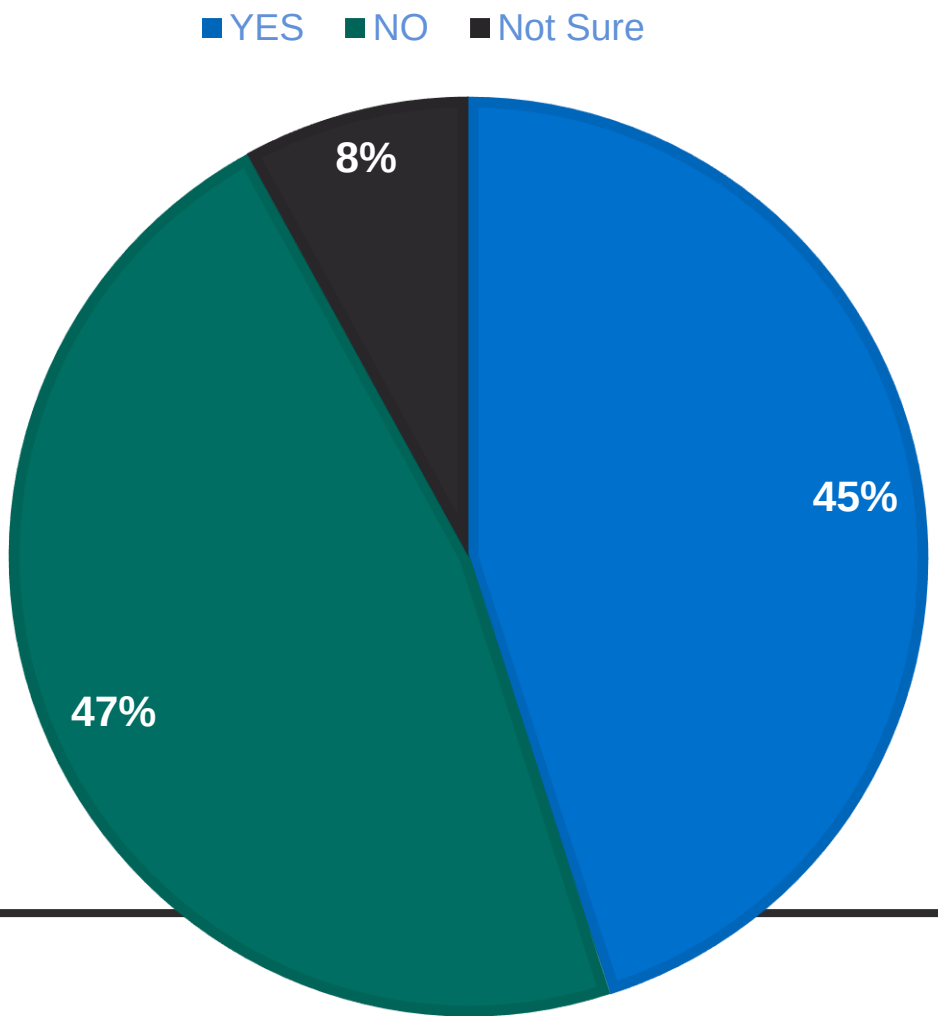


Q - If you have taken multiple drugs for RA overtime, please indicate which drugs you took first, second, etc. n=596

Champion of Yes

Utilization Management: Step Therapy

"HAVE YOU EVER BEEN TOLD THAT YOU HAD TO GO THROUGH A STEP THERAPY PROCESS FOR YOUR PRESCRIPTION MEDICATION NEEDS?"



Impact of Innovative Therapies on Rheumatoid Arthritis Patients

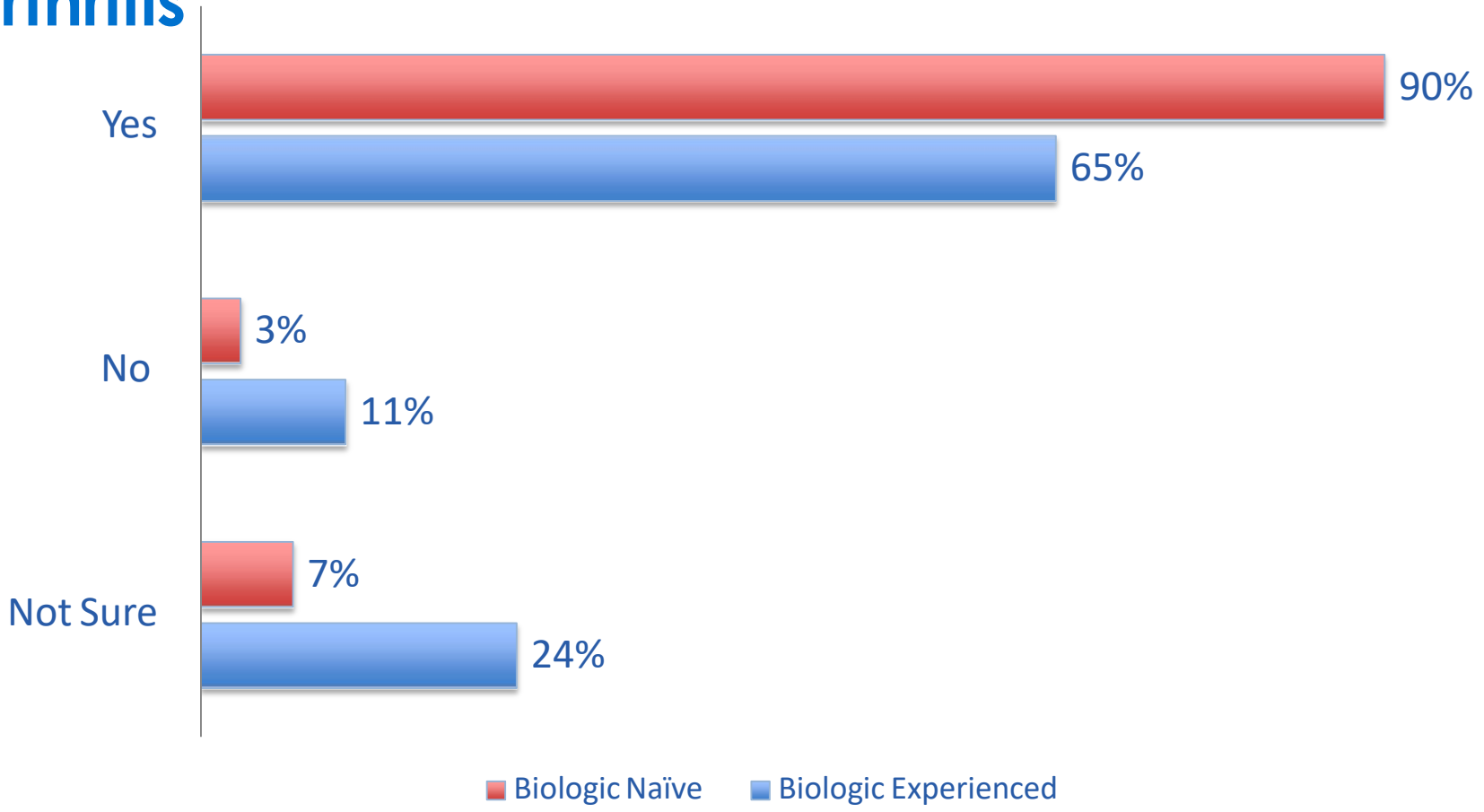
Survey 2

Arthritis Foundation℠

Methodology

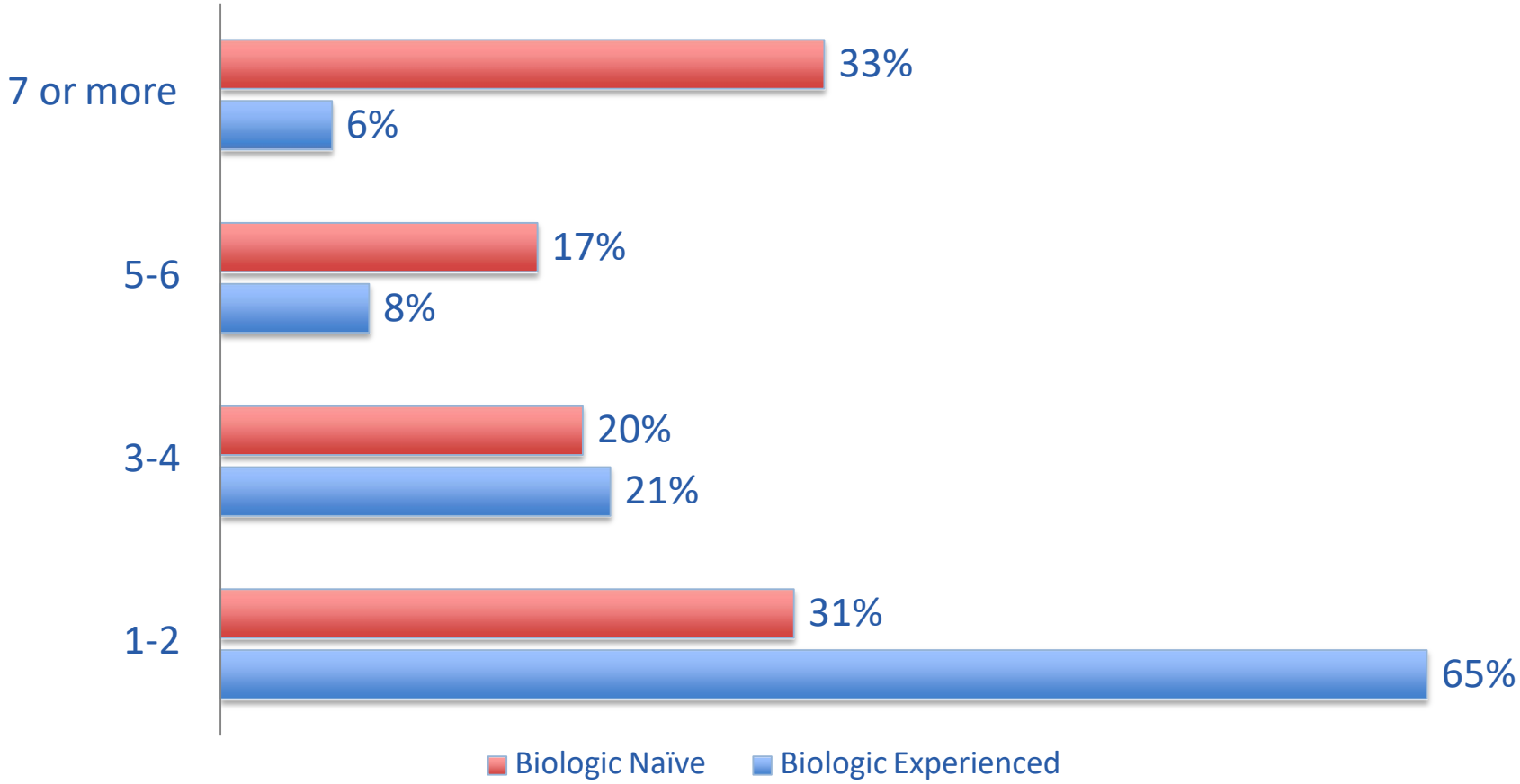
- Delivery method: Online survey; Qualtrics software
- Population: Arthritis Foundation constituents with rheumatoid arthritis
- Dates open: November 29 – December 1, 2016
- Total responses: *n*=**559**
  - Biologic Naïve: *n*=222
    - **Biologic naïve** for 5 years or more
  - Biologic experienced *n*=337
    - **Biologic experienced** within 5 years

Biologic naïve patients were 38% more likely to have experienced joint damage because of their arthritis



Biologic naïve for at least 5 years (n=222); Biologic experienced within 5 years (n=337)
Q. Have you experienced joint damage because of your arthritis?

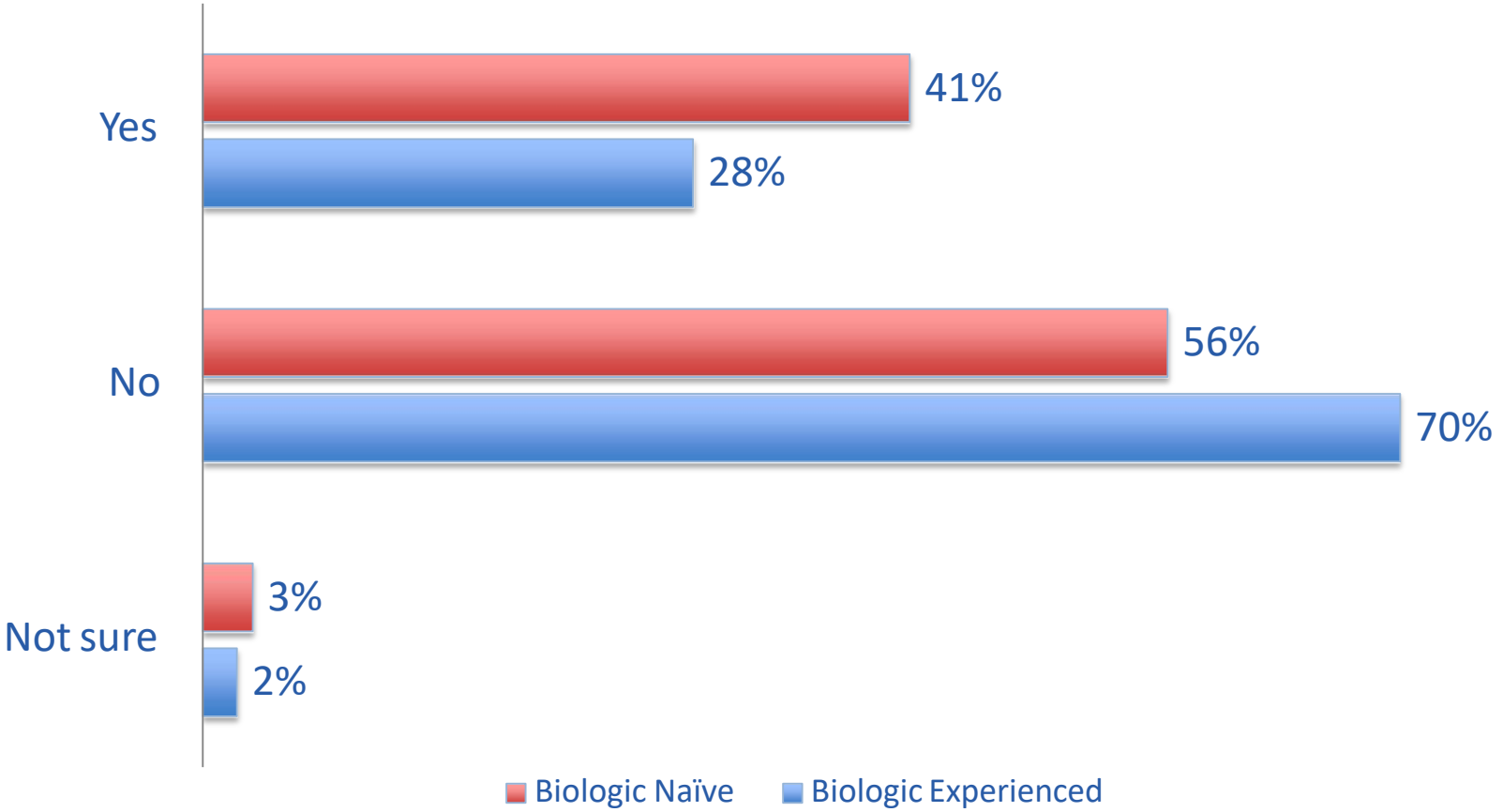
Biologic naïve patients were over 400% more likely to have had 7 or more joint replacements or other major surgeries such as a fusion



Biologic naïve for at least 5 years (n=222); Biologic experienced within 5 years (n=337)
Q. How many joint surgeries or fusions have you had?

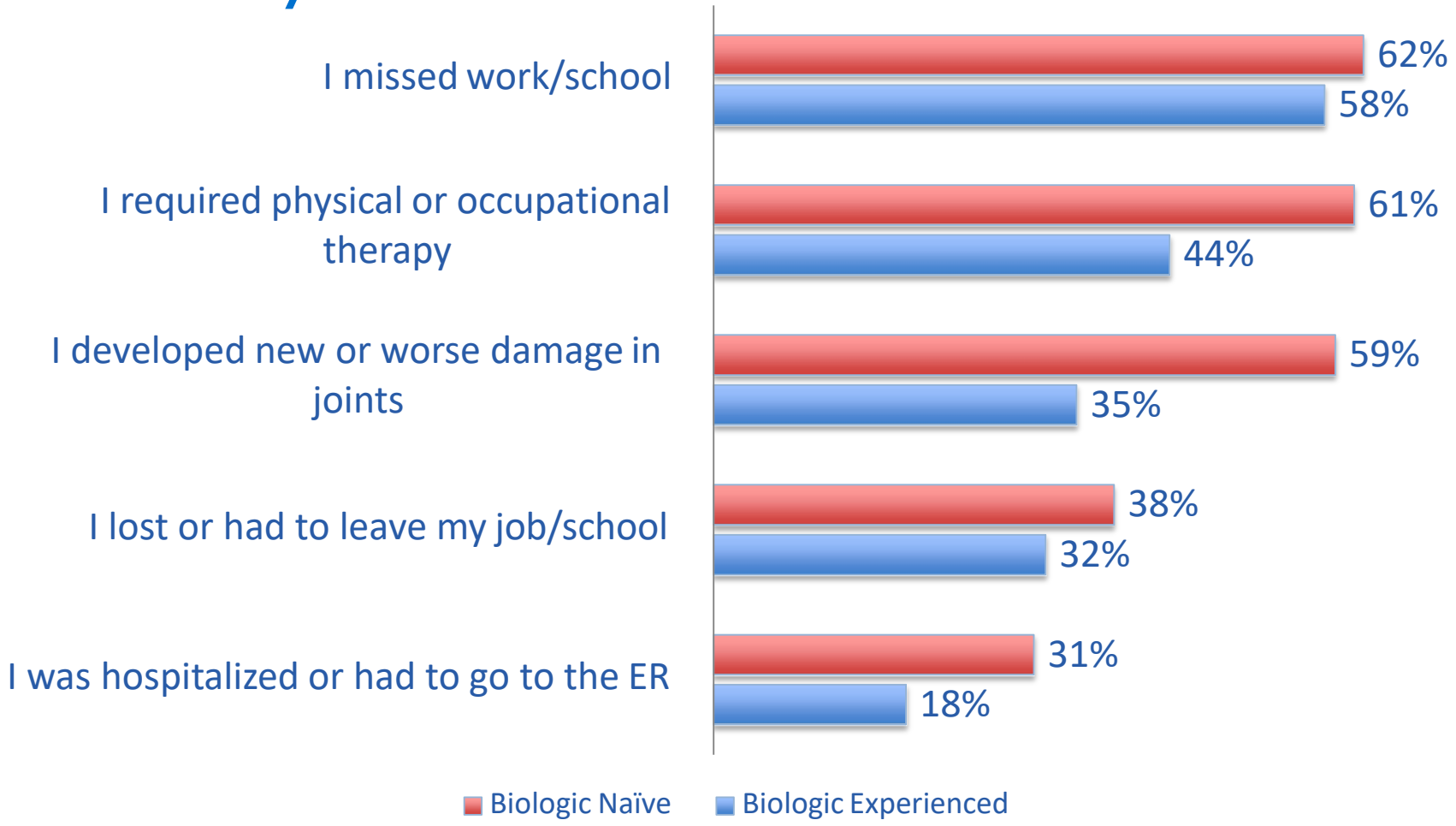
Champion of Yes

Biologic naïve patients are 44% more likely to report going on disability



Biologic naïve for at least 5 years (n=222); Biologic experienced within 5 years (n=337)
Q. Have you EVER had to go on disability?

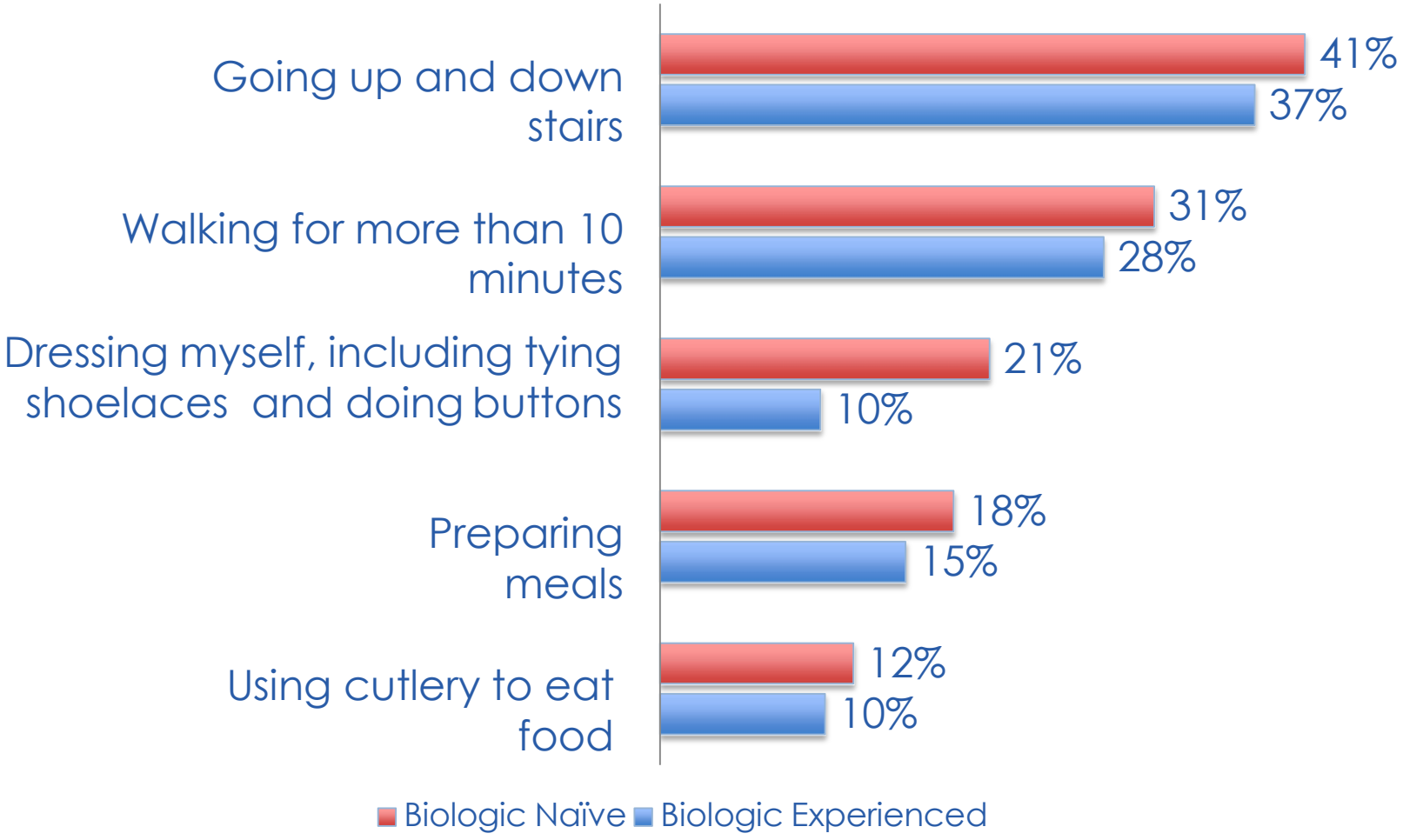
Biologic naïve patients were 66% more likely to be hospitalized or visit the ER when their disease was not well controlled by medication



Champion of Yes

Biologic naïve for at least 5 years (n=222); Biologic experienced within 5 years (n=337)
Q. Have you EVER experienced the following impacts when your disease was not well controlled while on medication? Please check all that apply.

Biologic naïve patients were more likely to indicate they have a "problem/major problem" with the following:



Biologic naïve for at least 5 years (n=222); Biologic experienced within 5 years (n=337)

Q. To what extent is each of the following a problem for you as a result of yourRA?

Summary

- RA is a **complex** disease requiring personalized, nuanced care
- Patients have to **cycle** through many treatments before becoming **stable**
- Patients need continued **access** to all treatments available

QUESTIONS?

Evidence Review

Dan Ollendorf, PhD

Chief Scientific Officer, ICER

ICER

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Key Review Team Members

Foluso Agboola, MBBS, MPH

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Patty Synnott, MALD, MS

We have no conflicts to disclose.

Topic in Context

Background: Rheumatoid Arthritis (RA)

- Most common chronic inflammatory arthritis in adults
- 1.3-1.8 million Americans affected
  - Occurs at any age; peak incidence at 50-60 years
  - More common in women
- Two key types of medication
  - Conventional DMARDs (e.g., methotrexate)
  - Targeted immune modulators (TIMs)
- Disease course
  - Progressive disability and shortened lifespan historically
  - Improvements in survival and other outcomes seen in era of earlier diagnosis and aggressive use of TIMs

RA in Context

- Complex disease to diagnose and manage
  - Multiple phenotypic and genotypic variations in pathogenesis of RA and response to treatment
- Evolution of management:
  - Aggressive treatment in patients with poor prognostic factors
  - Close surveillance of disease activity, frequent adjustments to treatment
  - Goal: Clinical remission or low levels of disease activity

Input from Patients and Patient Groups

- Insurance requirements/limits on therapy sequencing/switching burdensome
- Self-injection may limit valuable provider interaction vs. clinic-based infusion
- Financial challenges include drug costs and care coordination, lost work/school time, etc.
- Additional patient-centric measures required on symptom control, side effects, ADLs, etc.
- RA is heterogeneous and labile – “point in time” measures do not capture this well

RA in Context: Ongoing Challenges

- Shortage of available rheumatologists
- Time to diagnosis issues
- Rising list prices for TIMs in recent years
  - Adalimumab and Etanercept: ↑ 70-80% in last three years (now currently ~$4,000/month)
  - Potential out-of-pocket exposure for Medicare patients: $1,600 - $4,500 annually

TIMs for RA

Class	Drug	Brand name	Administration
TNF Inhibitors	**Adalimumab**	Humira	SC
	Certolizumab Pegol	Cimzia	SC
	Etanercept	Enbrel	SC
	Golimumab	Simponi, Simponi Aria	SC or IV
IL-6 inhibitor	**Sarilumab**	Kevzara	SC
	Tocilizumab	Actemra	SC or IV
JAK inhibitors	**Baricitinib**	Olumiant	PO
	Tofacitinib	Xeljanz	PO
IL-6 inhibitor	**Tocilizumab**	Actemra	SC or IV
JAK inhibitors	**Baricitinib**	Olumiant	PO
	Tofacitinib	Xeljanz	PO

Evidence Review

Overview

- **Target population**: moderately-to-severely active RA who experienced inadequate response to previous methotrexate or other conventional DMARD therapy
- **Interventions**: Combination therapy (TIM + conventional DMARD) or TIM monotherapy with 11 TIMs
- **Comparisons of interest**:
  - Head-to-head studies between TIMs
  - Conventional DMARD therapy alone

Key Outcomes

- Disease activity and remission (DAS28, CDAI, SDAI)
- Treatment response (ACR20, ACR50, and ACR70)
- Radiographic progression (modified total Sharp score)
- Function (HAQ-DI)
- *Patient-reported outcomes (pain, fatigue, HrQoL)*
- *Productivity loss and healthcare utilization*
- Harms

The Evidence

- 67 RCTs (8 head-to-head between TIMs), 17 observational studies
- Most of good quality
- Strong internal validity but early rescue and crossover from cDMARD arms (12-24 weeks) limits longer-term conclusions
- Challenges posed by use of different variants of certain measures (e.g., disease activity, radiographic progression) and their evolution over time

TIMs vs. Conventional DMARDs

- Studied most frequently in TIM-naïve or mixed (≥80% naïve) populations
- All TIMs generated statistically- and clinically-significant improvements over cDMARDs alone:
  - NNTs to achieve clinical remission of 20 or less for all TIMs
  - ≥90% increase in proportion of patients achieving ACR20 or better response (52-71% vs. 27%)
- Benefits seen for both combination and monotherapy approaches

Head-to-Head Studies of TIMs: Overview

- 8 head to head RCTs involving 9 TIMs
- Adalimumab the comparator in all but one trial
- 4 trials involved the newer IL-6 and JAK inhibitors

Head-to-Head RCTs of TIMs vs. Adalimumab: Combination Therapy

	n	Low Disease Activity/ Remission	ACR Response	Radiographic Progression	HAQ-DI
Abatacept (SC)	646	↔	↔	↔	↔
Tofacitinib	717	↔	↔	ND	↔
Baricitinib	1307	↑	↑	↔	↑
Certolizumab Pegol	915	↔	↔	ND	↔
Etanercept	125	↔	ND	ND	ND

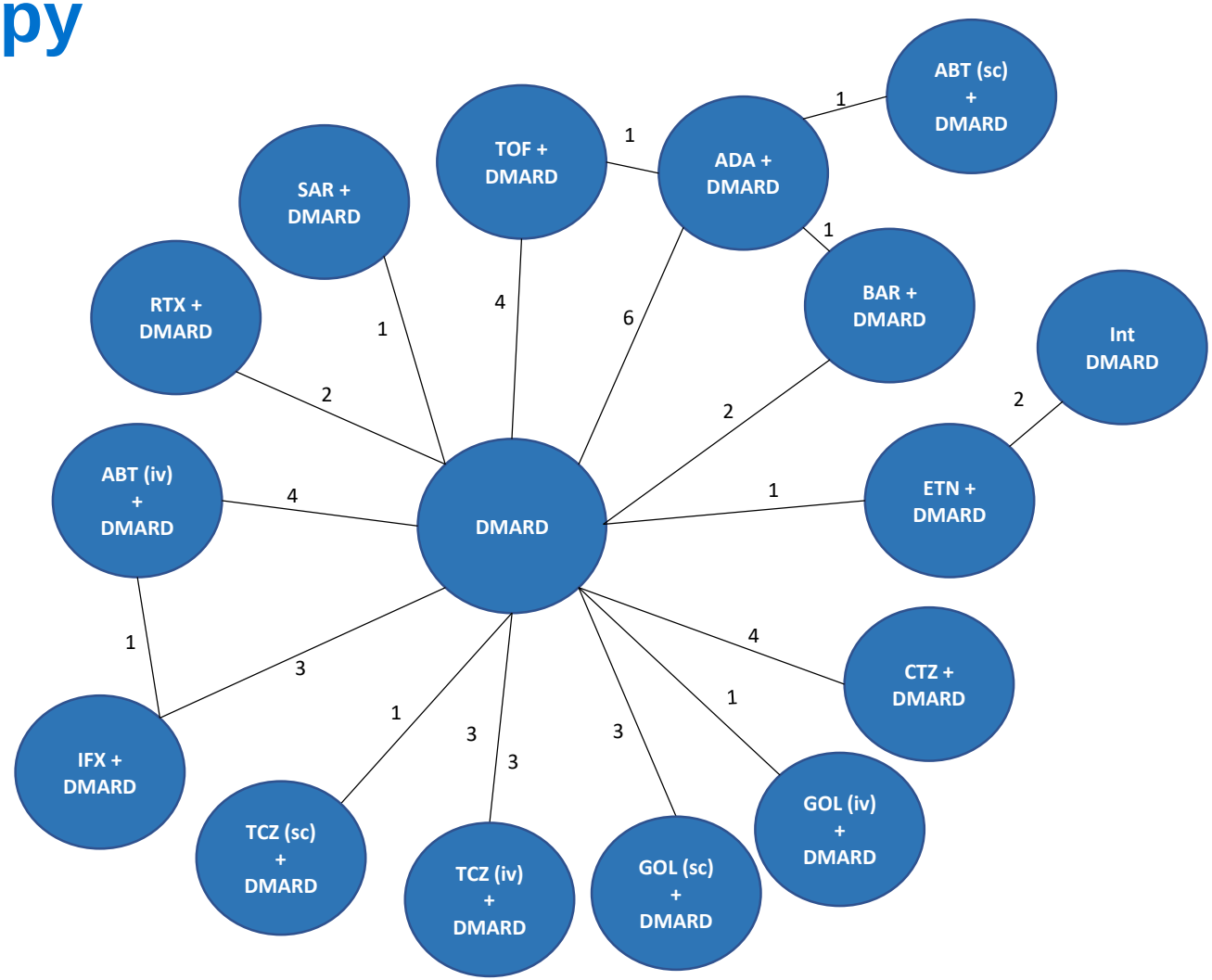
Superior	↑
Comparable	↔
Inferior	↓
No Data Identified	ND

Head-to-Head RCTs of TIMs vs Adalimumab: Monotherapy

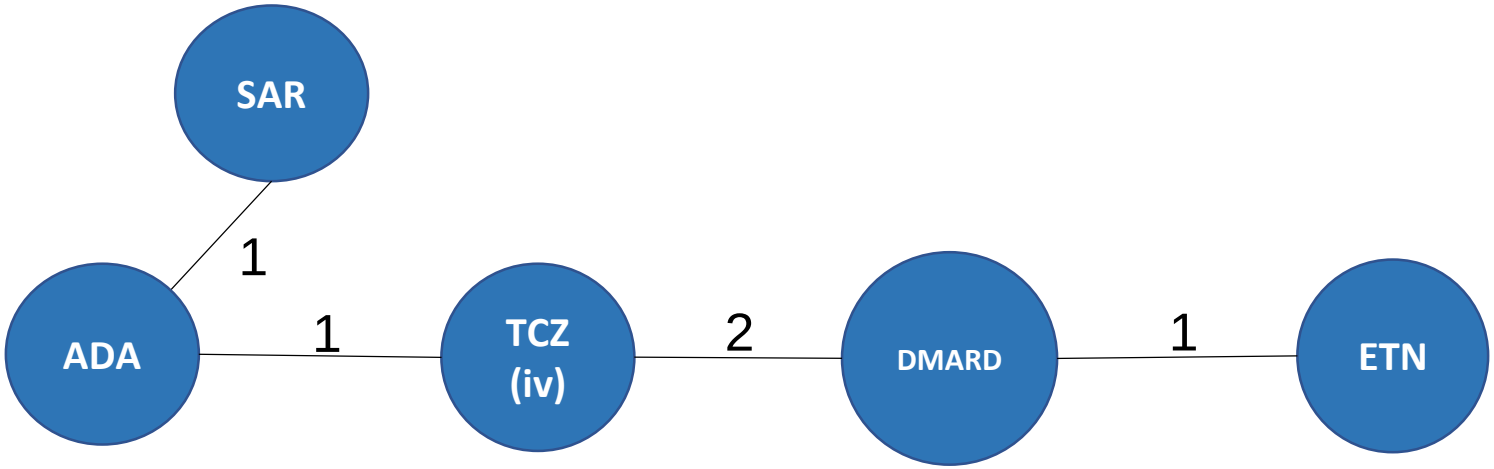
	n	Low Disease Activity/ Remission	ACR Response	Radiographic Progression	HAQ-DI
Sarilumab	369	↑	↑	ND	↑
Tocilizumab	326	↑	↑	ND	↔

Superior	↑
Comparable	↔
Inferior	↓
No Data Identified	ND

Network Meta-Analysis: Combination Therapy



Network Meta-Analysis: Monotherapy



Network Meta-Analyses

- No statistical differences between TIMs when used in combination with cDMARDs
- Greater likelihood of ACR response with tocilizumab and sarilumab monotherapy vs. adalimumab
  - Echoes results of head-to-head studies
- Findings consistent with other published SRs and NMAs

Harms

- Frequently reported adverse events: mild infections, injection site reactions, and infusion reactions
- Overall incidence of serious AEs, serious infections, malignancies, and deaths comparable between TIMs
- Serious infection in longer-term trials somewhat higher with infliximab (9 per 100 P-Y vs. 2-3 for other TIMs)
- Long-term observational data primarily for TNFα inhibitors:
  - No consistent or material differences in available studies

Black Box Warnings

- All FDA-approved TIMs (except abatacept) have black box warnings
- Tocilizumab
  - Serious infection
- Tofacitinib
  - Serious infection, lymphoma/malignancy, lymphoproliferative disorder in renal transplant patients
- TNFα-inhibitors,
  - Serious infection, lymphoma/malignancy (primarily children & adolescents)
- Rituximab
  - Fatal infusion reactions, severe mucocutaneous reactions, Hepatitis B reactivation, PML

Controversies & Uncertainties

- Head-to-head data from only 8 of 67 RCTs
- Patients do not feel that current PRO tools sufficiently capture their experience
- Need to identify predictors of treatment response
- Early crossover in DMARD-controlled trials may limit conclusions w/r/t longer-term outcomes
- Limited and emerging data on the effects of treatment sequencing, dose tapering, etc.
- Long-term effects of prolonged immunomodulation not well-understood for all TIMs

ICER Evidence Ratings (vs. Adalimumab)

	Intervention	Rating
Monotherapy	Sarilumab	**B+**
	Tocilizumab	**B+**
Combination Therapy	Baricitinib	**C+**
	Tofacitinib	**C**
	Abatacept (sc)	**C**
	Certolizumab pegol	**C**
	Etanercept	**C**

Other Benefits or Disadvantages

- Rapid return to function and work for certain patients and their caregivers
- Downstream clinical benefits (e.g., reduced need for disability aids, joint replacement)
- Availability of 5 distinct classes of TIMs critical, given frequent switch patterns observed
- Routes of administration
  - Baricitinib and Tofacitinib are oral agents, may be preferable for those with concerns about self-injection or infusion

Summary

- Evidence base accumulated over ~20 years documents substantial benefits of TIM therapy over conventional DMARDs alone
- IL-6 and JAK inhibitors comparable or superior to adalimumab in head-to-head studies
  - Greater uncertainly on long-term safety
- Outside of head-to-head trials vs. adalimumab, evidence not adequate to distinguish TIM effectiveness or safety

Public Comments Received

- Over-reliance on RCT data to inform evidence base, despite availability of RWE
- Step therapy requirements not just economically-driven; may reflect certainty in long-term safety, for example
- Differences in trial populations biases NMA
- Some trials originally described as head-to-head were not
- ICER report draws conclusions primarily based on ACR response

Long-term Cost-Effectiveness

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Department of Clinical Pharmacy
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Acknowledgements and Disclosures

- Collaborators:
  - Melanie Whittington, University of Colorado
  - R. Brett McQueen, University of Colorado
  - Varun Kumar, ICER
  - Rick Chapman, ICER
  - Dan Ollendorf, ICER

- The University of Colorado researchers report no industry funding related to rheumatoid arthritis.

Objective

To model the costs and outcomes for 11 targeted immune modulators (TIMs) relative to conventional disease-modifying anti-rheumatic drugs (cDMARDs) for adults with moderately-to-severely active rheumatoid arthritis.

Methods in Brief

Methods Overview (1)

- Population: Adults (average age 55 years) with moderately-to-severely active rheumatoid arthritis and inadequate response to or intolerance to prior therapy
- Setting: United States
- Perspective: Payer (direct medical care and drug costs)
- Comparators: Conventional DMARDs alone; and adalimumab (market leader)
- Time Horizon: Lifetime
- Discount Rate: 3% per year (costs and outcomes)

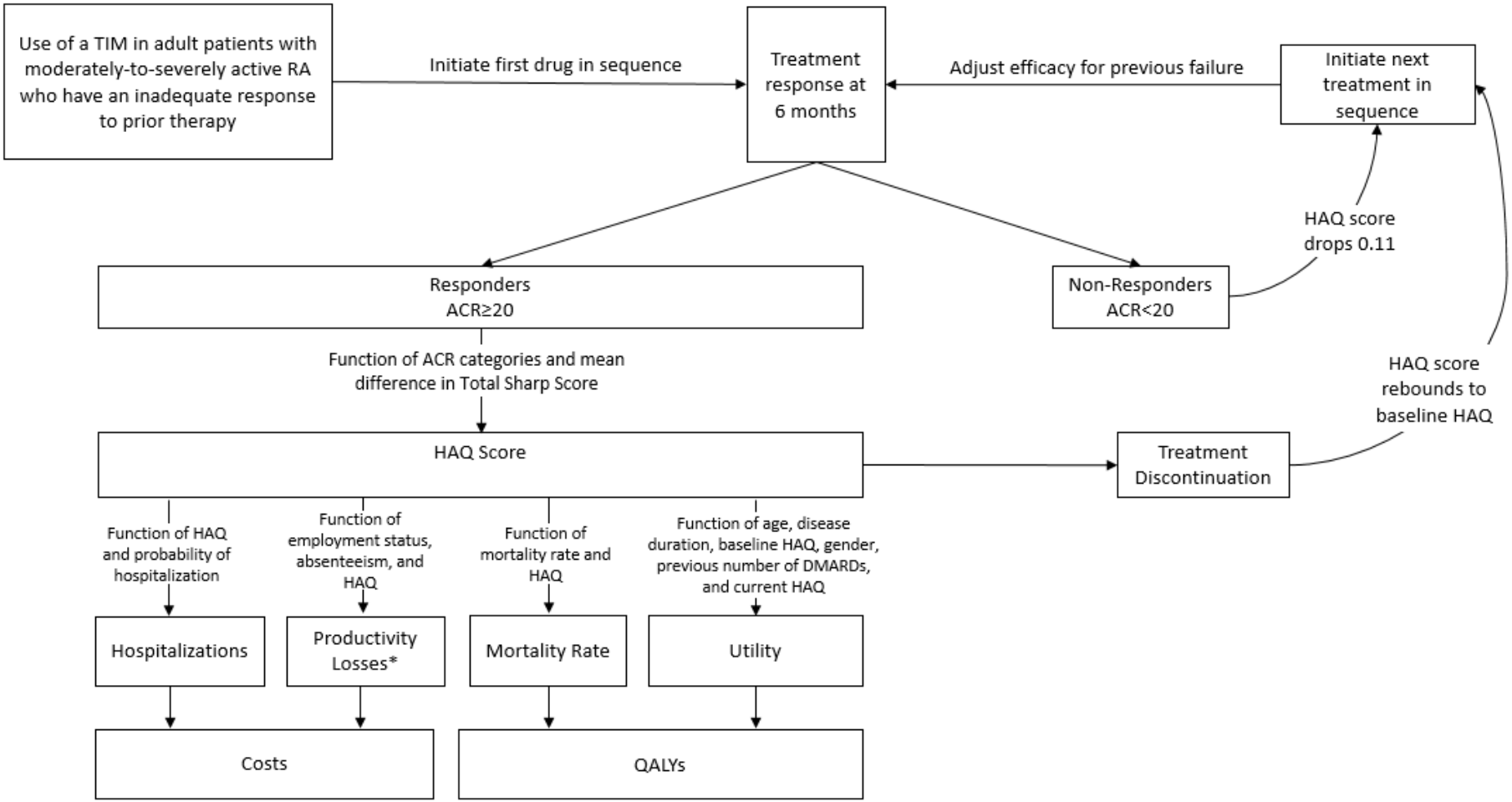
Methods Overview (2)

- Model: Sequential treatment cohort model (Markov cohort model)

- Cycle Length: 6 months

- Primary Outcome: Cost per quality-adjusted life year (QALY) gained
  - QALYs derived from Healthcare Assessment Questionnaire (HAQ) for Rheumatoid Arthritis score
  - HAQ score is a function of American College of Rheumatology (ACR) improvement criteria and modified Total Sharp Score (mTSS)

Model Schematic

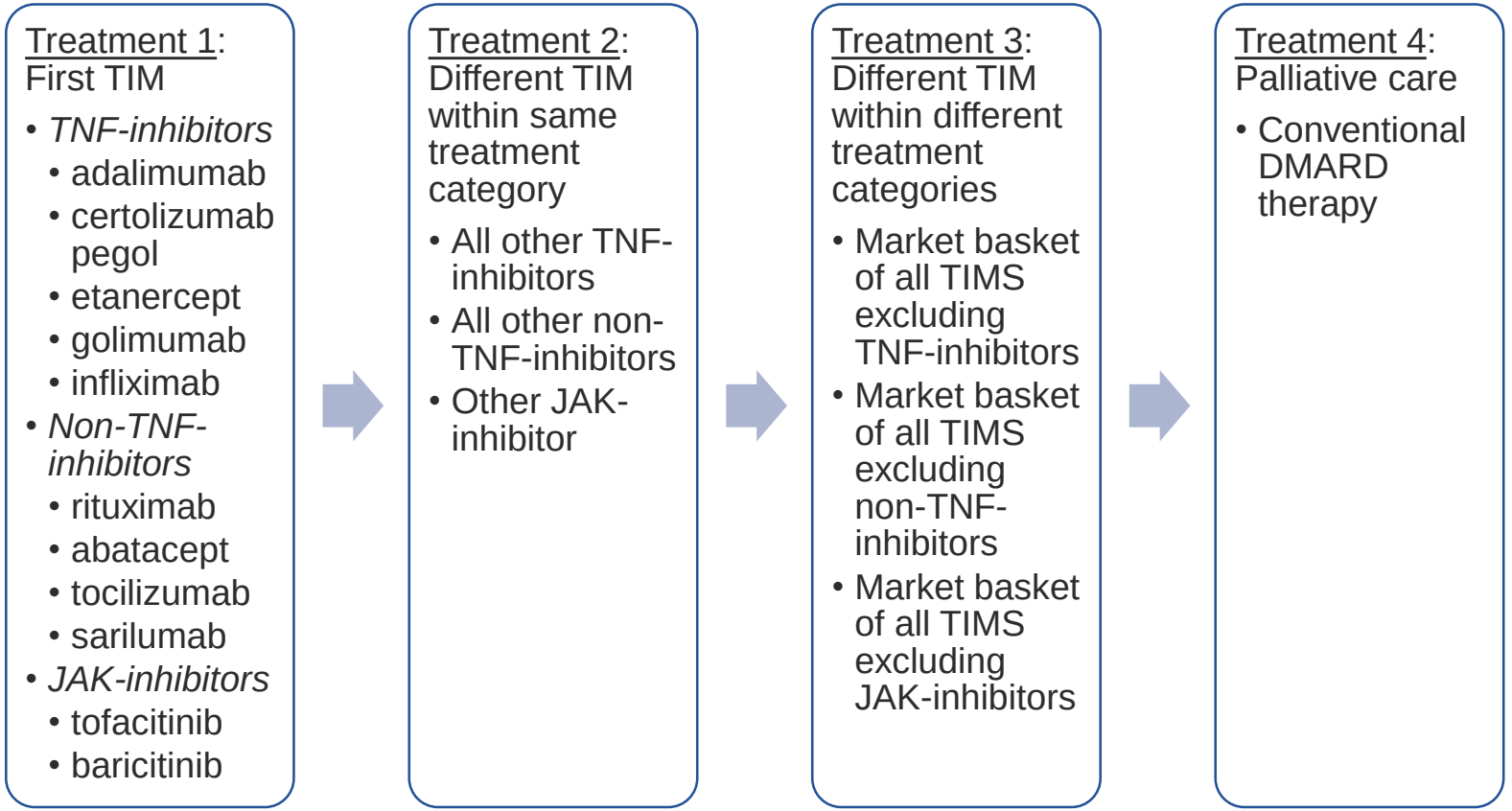


* Productivity losses are only included in a societal perspective (not payer perspective)

Key Model Assumptions

- Longer time on conventional DMARD therapy alone was associated with larger HAQ degradations (linear assumption).
- Longer time on a TIM was associated with larger mTSS benefits (linear assumption).
- Patients could discontinue treatment for two reasons:
  1. Lack of effectiveness,
  2. Occurrence of an adverse event.
- Efficacy of subsequent TIM treatments is assumed to be reduced (Hazard ratio: 0.84).

Model Sequential Treatment Pattern



Parameters: Discontinuation and Serious Adverse Events

- TIM discontinuation due to adverse events ranged from 3.5% to 7.4% per year (review of clinical trial literature).
- Serious adverse events were modeled by TIM, based on a review of the literature.
  - A serious infection case was assigned a disutility of -0.16 for one month and $13,747 (assumed 2/3 pneumonia; 1/3 cellulitis).
  - A tuberculosis case was assigned a disutility of -0.16 for two months and a cost of $12,220.

Parameters: Drug Cost

Intervention	Route	Discounted WAC*	Annual Drug Cost‡
rituximab	IV	$710	$30,764
abatacept	IV	$691	$27,637
abatacept	SC	$814	$42,306
tocilizumab	IV	$76	$27,627
tocilizumab	SC	$719	$21,861
sarilumab**	SC	----------	----------
tofacitinib	ORAL	$60	$43,873
baricitinib**	ORAL	----------	----------
adalimumab	SC	$1,554	$40,415
certolizumab pegol	SC	$1,288	$34,775
etanercept	SC	$777	$40,422
golimumab	SC	$2,905	$34,863
golimumab	IV	$1,114	$29,719
infliximab	IV	$817	$28,906
cDMARD (methotrexate)	ORAL	Generic	$1,155

*WAC as of February 2017, discounted to match SSR Health discounts by class;

**For investigational drugs, no annual cost was assumed, except the cost needed to achieve thresholds;

‡Annual drug cost only includes cost of drug therapy, and not any costs associated with administration or monitoring. Annual drug costs reported in this table were average over three years of treatment, assuming 100% compliance to reduce variation of loading dosing schedule.

Model Results

Base-Case for TIMs + Conventional DMARDs

Treatment 1	Drug Cost	Total Payer Cost	Average HAQ	Life Years	QALYs
rituximab	$366,768	$464,864	1.25	16.79	12.70
abatacept (iv)	$367,724	$466,733	1.22	16.82	12.78
abatacept (sc)	$452,292	$566,053	1.18	16.87	12.90
tocilizumab (iv)	$369,876	$470,205	1.19	16.85	12.88
tocilizumab (sc)	$329,324	$424,674	1.21	16.83	12.81
sarilumab	-	-	1.21	16.83	12.81
tofacitinib	$467,784	$579,140	1.28	16.75	12.57
baricitinib	-	-	1.25	16.78	12.67
adalimumab	$425,929	$530,720	1.25	16.78	12.68
certolizumab pegol	$417,742	$522,473	1.20	16.84	12.86
etanercept	$470,007	$583,449	1.12	16.94	13.12
golimumab (sc)	$408,413	$512,875	1.25	16.79	12.69
golimumab (iv)	$386,971	$488,380	1.23	16.81	12.75
infliximab	$381,243	$480,448	1.24	16.79	12.73
cDMARD	$18,209	$67,819	1.78	16.16	10.69

Results for TIMs as Monotherapy

Treatment 1	Drug Cost	Total Payer Cost	Average HAQ	Life Years	QALYs
tocilizumab (iv)	$384,441	$489,541	1.05	17.03	13.35
sarilumab	-	-	1.07	17.00	13.28
adalimumab	$449,224	$562,748	1.17	16.89	12.95
etanercept	$469,981	$584,952	1.11	16.95	13.16
cDMARD	$18,235	$67,525	1.76	16.18	10.75

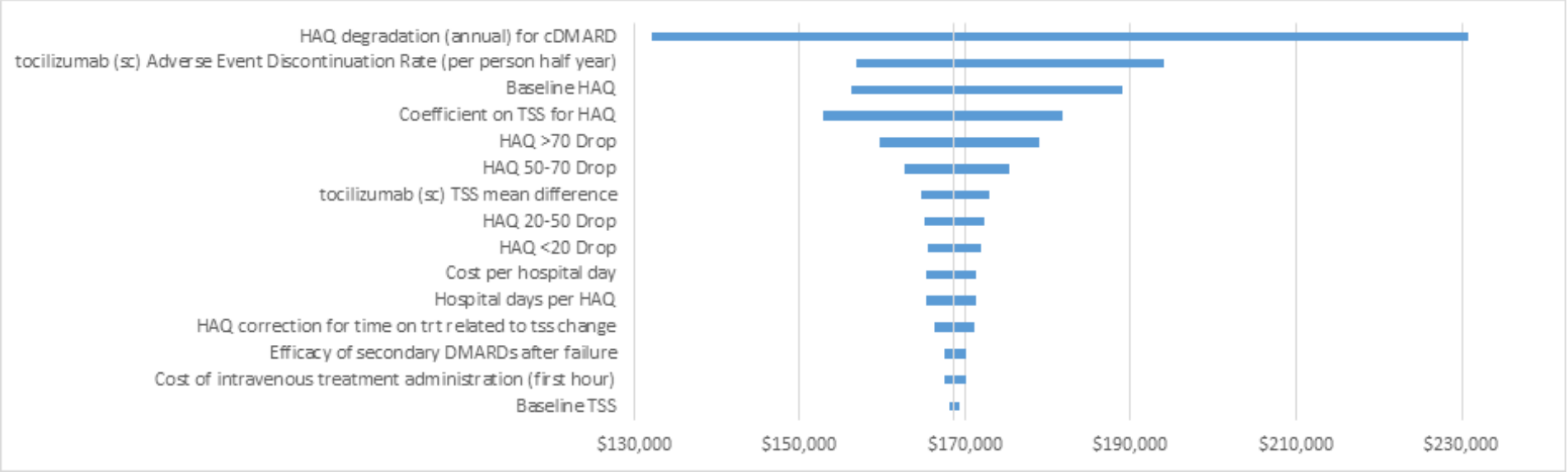
Incremental Cost-Effectiveness Ratios for the Base Case, TIMs + conventional DMARD

Treatment 1	ICER (cost per QALY gained) Comparator: cDMARD	ICER (cost per QALY gained) Comparator: adalimumab
rituximab	$198,056	Less costly, More effective
abatacept (iv)	$191,317	Less costly, More effective
abatacept (sc)	$225,853	$163,376
tocilizumab (iv)	$183,949	Less costly, More effective
tocilizumab (sc)	$168,660	Less costly, More effective
tofacitinib	$271,749	More costly, Less effective
adalimumab	$232,644	Reference
certolizumab pegol	$209,736	Less costly, More effective
etanercept	$212,021	$119,233
golimumab (sc)	$222,380	Less costly, More effective
golimumab (iv)	$204,212	Less costly, More effective
infliximab	$202,824	Less costly, More effective

Incremental Cost-Effectiveness Ratios for TIMs as Monotherapy

Treatment 1	ICER (cost per QALY gained) Comparator: cDMARD	ICER (cost per QALY gained) Comparator: adalimumab
tocilizumab (iv)	$162,038	Less costly, More effective
adalimumab	$225,423	Reference case
etanercept	$214,427	$102,697

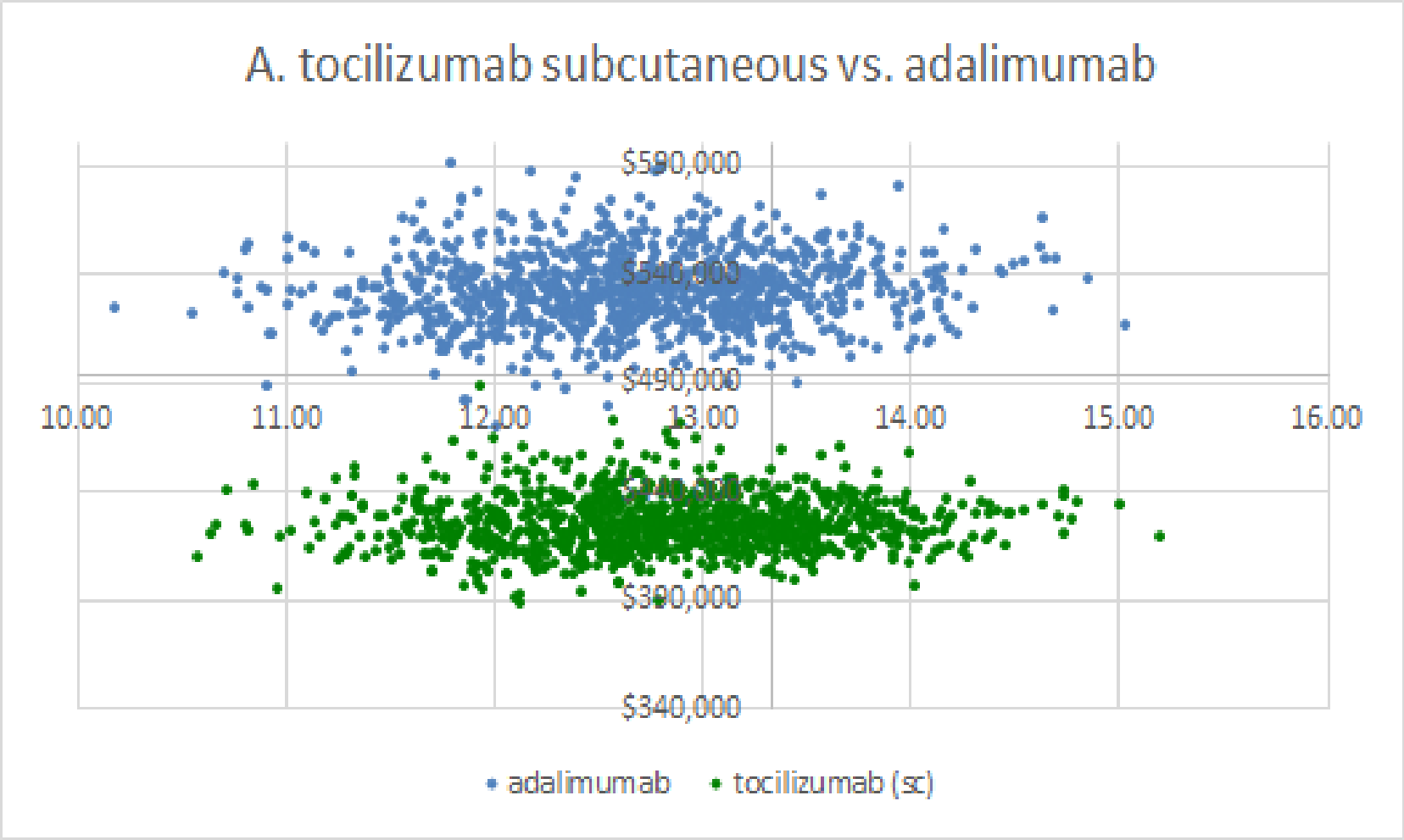
Tornado Diagram for Tocilizumab Subcutaneous versus Conventional DMARD



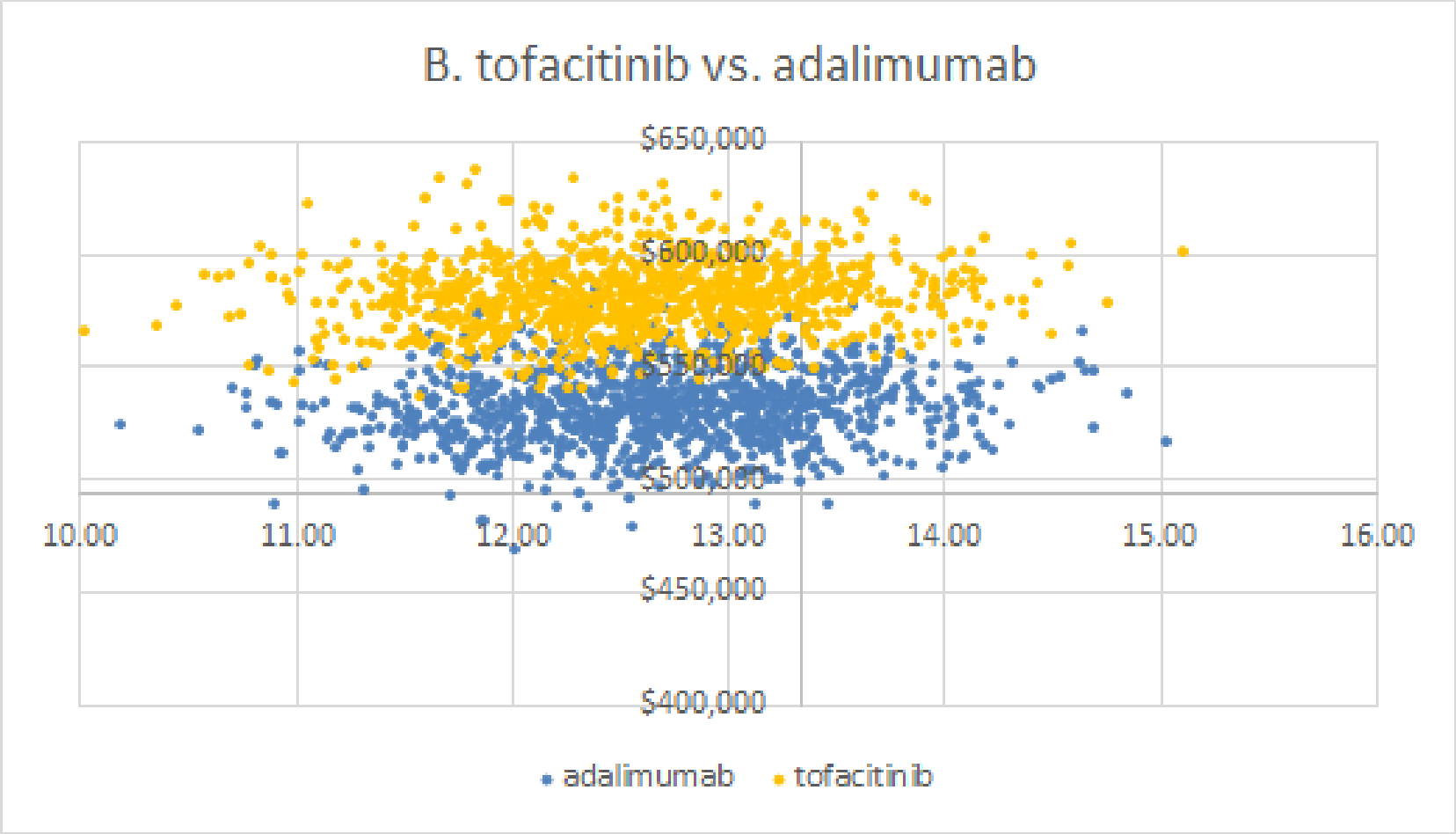
Probabilistic Sensitivity Analysis (PSA) Results: TIMs vs. conventional DMARD therapy

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY
rituximab	0%	0%	4%
abatacept (iv)	0%	0%	4%
abatacept (sc)	0%	0%	0%
tocilizumab (iv)	0%	0%	10%
tocilizumab (sc)	0%	0%	27%
tofacitinib	0%	0%	0%
adalimumab	0%	0%	0%
certolizumab pegol	0%	0%	1%
etanercept	0%	0%	1%
golimumab (sc)	0%	0%	0%
golimumab (iv)	0%	0%	1%
infliximab	0%	0%	2%

PSA Results: Cost-Effectiveness Clouds Tocilizumab (sc) vs. Adalimumab (Comb. w/MTX)



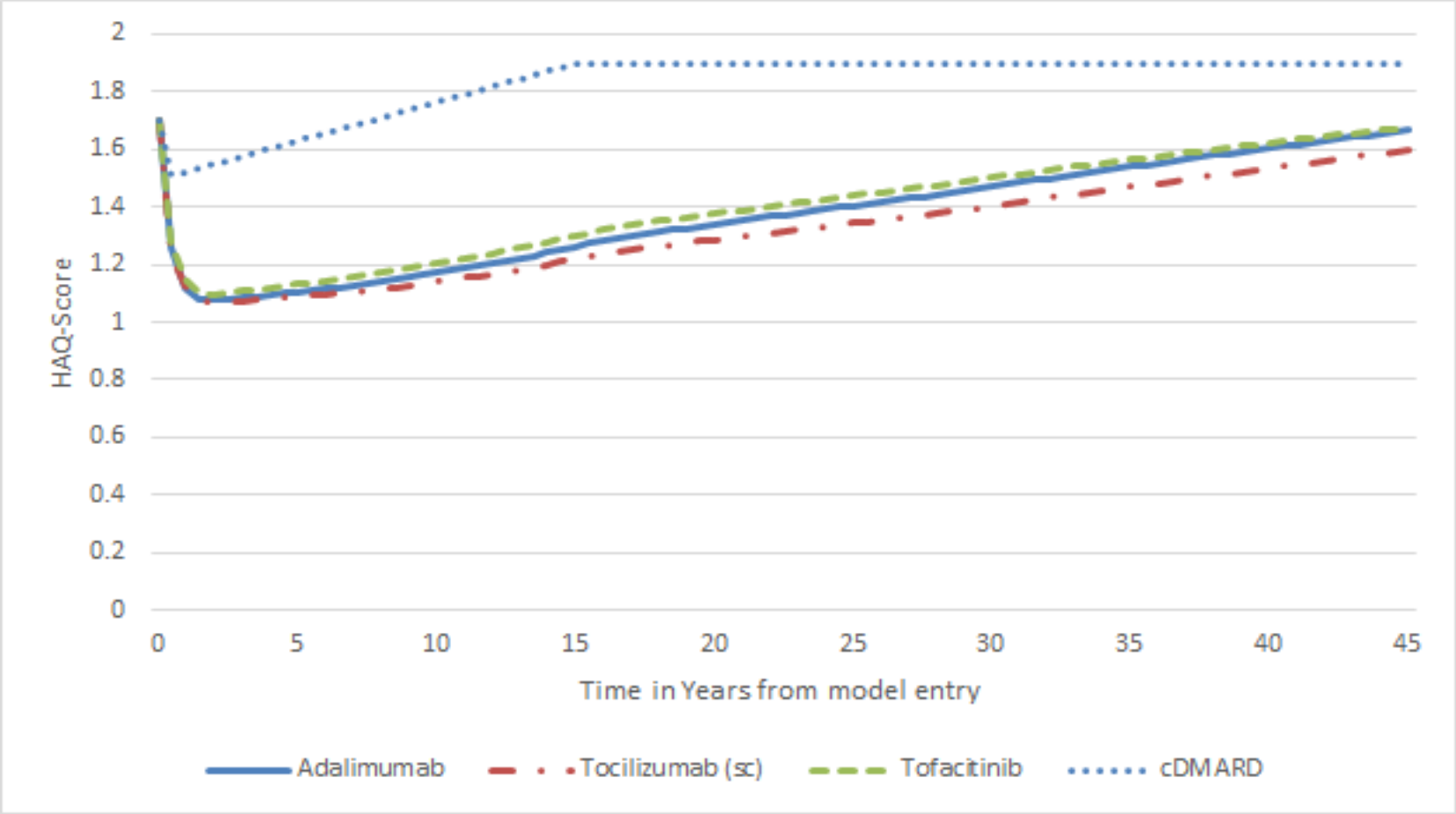
PSA Results: Cost-Effectiveness Clouds Tofacitinib vs. Adalimumab (Comb. w/MTX)



Scenario Analysis Results

- Treatment 4 as Market Basket TIM resulted in slightly higher costs per QALY (vs. base-case).
- Societal perspective resulted in lower costs per QALY with tocilizumab (iv and sc) yielding costs per QALY in the $130,000 - $140,000/QALY range.
- Short-term time horizon findings were higher than base-case and were $75,000 - $125,000 per additional responder after year one.
- Experienced TIM population findings were slightly lower compared to base-case, but remained above $150,000/QALY.

Consequences of Treatment throughout Model Time Horizon



Limitations

- In clinical practice, treatment choice is often based on patients' individual characteristics and risk factors, which may not be consistent with the model's sequential treatment pattern.
- One universal hazard ratio for the reduced efficacy of subsequent treatments was assumed, due to the limited drug class-specific data available.
  - This reduced efficacy was tested in a one-way sensitivity analysis and suggested limited impact on the findings.
- Sequential patterns tended to move the cost-effectiveness findings closer to the average TIM with less possible separation across TIMs.
  - The sequential patterns within TIMs appears close to observations within registries of TIM discontinuation and switching.
- Uncertainty remains surrounding the long-term progressions of HAQ degradation for conventional DMARD and mTSS improvements for TIMs.

Summary

- Base-case findings suggest that all TIMs provide substantial clinical benefit in comparison to conventional DMARDs alone; their additional costs translate into cost-effectiveness estimates ranging from approximately $170,000 to $270,000 per QALY gained.
- Compared to the market leader adalimumab, most TIMs in combination with conventional DMARDs were more favorable.
- One-way sensitivity analyses suggested that annual HAQ degradation for conventional DMARDs was the most influential parameter.
- Probabilistic sensitivity analyses suggested that separation across TIMs appeared to be more in the cost domain rather than in the QALY domain.

Public Comments Summary

- Where possible, add more transparency and evidence of model validation
- Use best available evidence for forecasting the long-term costs and consequences of TIMs as well as conventional DMARDs
- Concerns over cohort model with limited patient-level heterogeneity
- TIM dosing was informed by trial evidence to connect the clinical signals with their corresponding cost

Public Comment: Manufacturer Representatives

Public Comment: Manufacturer Representatives

Name	Title	Company
Margaret Michalska, MD	Associate Group Medical Director	Genentech
Brad Stolshek, Pharm.D.	Director, Global Health Economics – Inflammation	Amgen
Tammy Curtice, PharmD, MS	Director, Health Economics & Outcomes Research	Bristol-Myers Squibb
Andrew Koenig D.O., F.A.C.R.	Inflammation & Immunology Group Lead	Pfizer
Andreas Kuznik, Ph.D.	Senior Director Health Economics and Outcomes Research	Regeneron Pharmaceuticals
Dr Jeff Stark	Head of Medical Affairs, Rheumatology	UCB

Public Comment

Dr. Christopher Phillips, American College of Rheumatology

Doctor

Conflicts of interest:

Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000

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If yes, please describe the relationship(s) below.

Abbvie - speaker bureau
Abbvie - clinical research

Dr. Liana Fraenkel, Professor of Medicine, Yale

Conflicts of interest:

None to disclose

Chantelle Marcial, Global Healthy Living Foundation—Member

Conflicts of interest:

Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000

Status or position as an officer, board member, trustee, owner or employee of a health care company, or an organization which receives more than 25% of its funding from health care companies
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Arthritis Foundation

Jen Melanson, Arthritis Foundation Advocate & Arthritis Patient
Renay Houlem, Arthritis Foundation Advocate & Arthritis Patient
Anna Legassie, Arthritis Foundation Advocate & Arthritis Patient

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Break for Lunch

Meeting will resume at 1:00PM

Voting Questions

1. Test Voting Question: The coldest day in Boston history was February 9th, 1934. What was the temperature on this day?

A. -22° F
B. -6° F
C. 0° F
D. -18° F

Patient Population

***Patient population for all voting questions**:* Patients age 18 and older with moderately-to-severely active rheumatoid arthritis and inadequate response to or intolerance of conventional DMARDs.

Comparative Effectiveness of Targeted Immune Modulators as Monotherapy

2. Is the evidence adequate to demonstrate that the net health benefit of tocilizumab monotherapy is superior to that provided by adalimumab monotherapy?

Yes **No**

3. Is the evidence adequate to demonstrate that the net health benefit of sarilumab monotherapy is superior to that provided by adalimumab monotherapy?

Yes **No**

4. Is the evidence adequate to distinguish the net health benefit between tocilizumab monotherapy and sarilumab monotherapy?

Yes **No**

5. Is the evidence adequate to demonstrate that the net health benefit of tofacitinib monotherapy is superior to that provided by adalimumab monotherapy?

Yes **No**

6. Is the evidence adequate to demonstrate that the net health benefit of baricitinib monotherapy is superior to that provided by adalimumab monotherapy?

Yes **No**

7. Is the evidence adequate to distinguish the net health benefit between tofacitinib monotherapy and baricitinib monotherapy?

Yes **No**

Comparative Effectiveness of Targeted Immune Modulators in Combination With cDMARDs

8. Is the evidence adequate to demonstrate that the net health benefit of tocilizumab + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes **No**

9. Is the evidence adequate to demonstrate that the net health benefit of sarilumab + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes **No**

10. Is the evidence adequate to distinguish the net health benefit between tocilizumab + cDMARD therapy and sarilumab + cDMARD therapy?

Yes **No**

11. Is the evidence adequate to demonstrate that the net health benefit of tofacitinib +cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes **No**

12. Is the evidence adequate to demonstrate that the net health benefit of baricitinib + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes **No**

13. Is the evidence adequate to distinguish the net health benefit between tofacitinib + cDMARD therapy and baricitinib + cDMARD therapy?

Yes **No**

Comparative Value of Targeted Immune Modulators (TIM)

14. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, **what is the long-term value for money for tocilizumab monotherapy in comparison to adalimumab monotherapy?**

A. **Low**
B. **Intermediate**
C. **High**

15. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, **what is the long-term value for money for tocilizumab + cDMARD therapy in comparison to adalimumab + cDMARD therapy?**

A. **Low**
B. **Intermediate**
C. **High**

16. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, **what is the long-term value for money for tofacitinib monotherapy in comparison to adalimumab monotherapy?**

A. **Low**
B. **Intermediate**
C. **High**

17. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, **what is the long-term value for money for tofacitinib + cDMARD therapy in comparison to adalimumab + cDMARD therapy?**

A. **Low**
B. **Intermediate**
C. **High**

Policy Roundtable

Policy Roundtable

Policy Roundtable	
Thomas Amoroso, MD, MPH Medical Director for Medical Policy Tufts Health Plan	**Himanshu R. Patel, D.O.** Sr. Medical Advisor, Musculoskeletal Medicine Eli Lilly and Company
Andreas Kuznik, PhD Senior Director of HEOR Regeneron Pharmaceuticals	**Sandie Preiss, MPA** National Vice President Arthritis Foundation
Andrew J. Laster, MD, FACR, CCD Board of Directors United Rheumatology Arthritis & Osteoporosis Consultants of the Carolinas	**Janet Stearns Wyatt, PhD, RN, FAANP** Patient, Volunteer for the Arthritis Foundation and Retired Nurse Practitioner
Matthew H. Liang, MD, MPH Professor of Medicine, Harvard Medical School Division of Rheumatology, Immunology, and Allergy Brigham and Women's Hospital	**Robert Zavoski, MD, MPH** Medical Director Connecticut Department of Social Services

New England CEPAC Reflections

Adjourn

Evidence Review

Dan Ollendorf, PhD

Chief Scientific Officer, ICER

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Extra Slides

T-cell inhibitors-Abatacept

- There were two abatacept head to head RCTs
  - Abatacept (sc) versus adalimumab (both in combination with methotrexate)
  - Abatacept (iv) versus infliximab (both in combination with methotrexate)
- Abatacept was similar to adalimumab and infliximab in rates of remission, ACR response, and improvement in HAQ-DI and other patient reported outcomes at 24 weeks
- No statistical difference between abatacept and adalimumab in slowing radiographic progression at 1 year

IL-6-Inhibitors- Tocilizumab

- One head to head RCT was identified of tocilizumab monotherapy versus adalimumab monotherapy
- Tocilizumab was superior to adalimumab in achieving:
  - **Low disease activity** (39.9% vs. 10.5%, p<.0001) and **clinical remission** (51.5% vs. 19.8%, p<0.0001) using DAS28-ESR at 24 weeks; CDAI and SDAI findings were similar
  - **ACR20** (65% vs. 49%, p=0.0038; ACR50 and ACR70 were similar)
- Tocilizumab did not differ from adalimumab in HAQ-DI improvement and most other patient reported outcomes

IL-6-Inhibitors- Sarilumab

- One head to head RCT was identified of sarilumab monotherapy versus adalimumab monotherapy
- Sarilumab was superior to adalimumab in achieving:
  - **Low disease activity** (42.9% vs. 14.1%, p<0.0001) and **clinical remission** (26.6% vs. 7%, p<.0001) using DAS28-ESR at 24 weeks; CDAI was similar
  - **ACR20** (72% vs. 58%; p=0.0074; ACR50 and ACR70 were similar)
  - **HAQ-DI improvement** (patients achieving MCID of 0.3: 62% vs. 47.6%, all p<0.01)

JAK-inhibitors- Tofacitinib

- One head to head RCT was identified of tofacitinib vs. adalimumab (both in combination with methotrexate)
- Tofacitinib was similar to adalimumab in rates of remission, ACR response, and improvement in HAQ-DI and other patient reported outcomes at 24 weeks

JAK-inhibitors-Baricitinib

- 1 head-to-head RCT of baricitinib + methotrexate vs. adalimumab + methotrexate
- Baricitinib was superior to adalimumab in achieving:
  - **Disease Activity/Remission:** no differences in low disease activity and clinical remission at week 24; at week 52, baricitinib significantly more low disease activity (CDAI, SDAI, DAS28-ESR) but not remission
  - **ACR Response:** ACR20 (74% vs. 66%; p≤0.05) and ACR70 response (30% vs. 22%; p≤0.05) at Week 24; ACR50 not significantly different
  - **HAQ-DI:** 73% vs. 64% achieved MCID; p<0.05
- There were no significant differences in radiographic progression at week 52

TNFα-Inhibitors- Adalimumab monotherapy

- 2 head-to-head RCTs: sarilumab vs. adalimumab and tocilizumab vs. adalimumab
- **Disease Activity/Remission**: Less remission with adalimumab using DAS28-ESR at 24 weeks
  - Sarilumab (7% vs. 27%, p≤0.0001)
  - Tocilizumab (10.5% vs. 39.9%, p<0.0001)
- **ACR Response**: Less response with adalimumab
  - Sarilumab (ACR20 58% vs. 72%, p=0.0074), ACR50 & ACR70 were similar
  - Tocilizumab (ACR20 49% vs. 65%, p=0.0038), ACR50 & ACR70 were similar
- **HAQ-DI**: Adalimumab and tocilizumab similar improvement
  - Less improvement than sarilumab (47.6% vs. 62% for MCID of 0.3, p<0.01)

TNFα-Inhibitors- Adalimumab Combination Therapy

- 5 head-to-head RCTs identified
- Similar to abatacept, etanercept, tofacitinib, and certolizumab pegol in rates of remission, ACR response, and improvement in HAQ-DI
- No statistical differences between abatacept and adalimumab or baricitinib and adalimumab in slowing radiographic progression
- Adalimumab inferior to baricitinib for ACR20 and ACR70, and HAQ-DI; evidence mixed for disease activity/remission

TNFα-Inhibitors- Certolizumab Pegol

- 1 head-to-head RCT of certolizumab pegol + methotrexate vs. adalimumab + methotrexate

- No difference between agents in low disease activity, remission, ACR response, or HAQ-DI over 104 weeks of follow-up

TNFα-Inhibitors- Etanercept

- 1 head-to-head RCT identified of etanercept + DMARD vs. adalimumab + DMARD
- Mean change in disease activity (DAS28-CRP) comparable
- Data on other key outcomes not reported

TNFα-Inhibitors- Infliximab

- 1 head-to-head RCT of infliximab + methotrexate vs. abatacept (iv) + methotrexate
- No statistical differences in the proportion of patients with low disease activity, clinical remission, or change in HAQ-DI at week 24.
- Fewer patients achieved ACR20 at year 1 with IFX (56% vs 72%; p≤0.05); statistical differences not detected for ACR50 and 70.

Important Patient-reported Outcomes

- **Quality of life**: Statistically significant differences in Physical Component Score (SF-36) favoring TIM treatment over DMARD consistently reported,
  - 45-76% of patients met or exceeded an MCID of 5 across studies.
  - Changes in Mental Component Score were more moderate, and did not consistently report significant differences between TIMs and DMARDs.
- **Pain:** Statically-significantly greater improvement with TIMs vs. DMARDs
  - 21.8 - 40.9 point improvement vs. 7.3 - 15.7 points (0-100 VAS scale)
- **Fatigue:** Statistically significant differences favoring treatment with a TIM over DMARD in all trials that reported on the FACIT-F.
  - 6.5-10.1 point improvement with a TIM vs. 2.2-point worsening to a 7.9-point improvement with DMARDs

Productivity

- Limited evidence
- Abatacept (sc) and adalimumab + methotrexate: similar improvements in absenteeism, reduced on-the-job effectiveness, work productivity loss, and activity impairment over two years of follow-up.
- Baricitinib and adalimumab combination therapy showed similar 52-week improvements in daily activity and work productivity
- Evidence from trials that compared TIMs to DMARDs was inconsistent for productivity/work loss changes.

Healthcare utilization and Caregiver Burden

- Limited evidence
- Etanercept + methotrexate vs. DMARD showed comparable proportions of patients visiting ED or a rheumatologist over 128 weeks of follow-up
- Requirements for caregiver assistance declined more with etanercept combination therapy.

TIMs vs. DMARDs (TIM-experienced population)

- Data from TIM-experienced populations were limited to 5 of the 11 TIMs: *Abatacept, baricitinib, rituximab, sarilumab, and tocilizumab*
- Only combination therapy evaluated
- Similar to TIM naïve populations, all produced statistically significant improvement in
  - Disease activity and remission (DAS28 at 24 weeks)
  - ACR response (ACR 20, 50 & 70 at 24 weeks)
  - HAQ-DI function and disability

Evidence from Observational Studies

- 3 registry studies compared adalimumab, etanercept, and infliximab
- **CORRONA Registry**: no significant differences in clinical remission or ACR response
- **Hellenic Registry**: No significant differences in rates of remission using DAS28-ESR, but greater remission with adalimumab using CDAI and SDAI definitions
  - CDAI: 15%[ADA] vs. 8% [IFX] vs. 7% [ETN], p=0.022
  - SDAI: 17% [ADA] vs. 8% [IFX] vs. 8% [ETN], p=0.009
- **DANBIO Registry**
  - Greater remission with adalimumab vs. infliximab (39% vs. 27%)
  - Greater ACR70 response for adalimumab (OR=2.05; 95% 1.52 to 2.76) and etanercept (OR=1.78; 95% CI 1.28-2.50) relative to infliximab

Network Meta-Analysis: Methods and Assumptions

- Assumptions
  - All conventional DMARDs have equivalent efficacy
  - Different types of administration of the same agents (i.e., iv vs. sc) may have differential performance
  - Incremental treatment effect is the same regardless of the ACR cut-off (i.e., 20 vs. 50 vs. 70)
- Random effects, multinomial likelihood model
- ACR20/50/70 response outcomes tabulated to create numbers of patients in mutually exclusive categories
- WinBUGS v1.4.3

Network Meta-Analysis Derived Proportions of Patients in Each ACR Response Category, by Combination Regimen: Mixed Population

Treatment	ACR <20	ACR 20-50	ACR 50-70	ACR 70-100
Etanercept + cDMARD	29%	23%	21%	27%
Certolizumab pegol + cDMARD	29%	23%	21%	26%
Tocilizumab (iv) + cDMARD	38%	23%	19%	19%
Sarilumab + cDMARD	40%	23%	19%	18%
Golimumab (sc) + cDMARD	41%	23%	18%	17%
Abatacept (iv) + cDMARD	42%	23%	18%	17%
Golimumab (iv) + cDMARD	42%	23%	18%	17%
Baricitinib + cDMARD	42%	23%	18%	16%
Tocilizumab (sc) + cDMARD	43%	23%	18%	16%
Abatacept (sc) + cDMARD	43%	23%	18%	16%
Infliximab + cDMARD	45%	23%	17%	15%
Adalimumab + cDMARD	45%	23%	17%	15%
Tofacitinib + cDMARD	47%	23%	17%	14%
Rituximab + cDMARD	48%	23%	16%	13%
Intensive cDMARD*	50%	23%	16%	12%
Conventional DMARD	73%	16%	8%	4%
*combination therapy with 2-3 conventional DMARDs				

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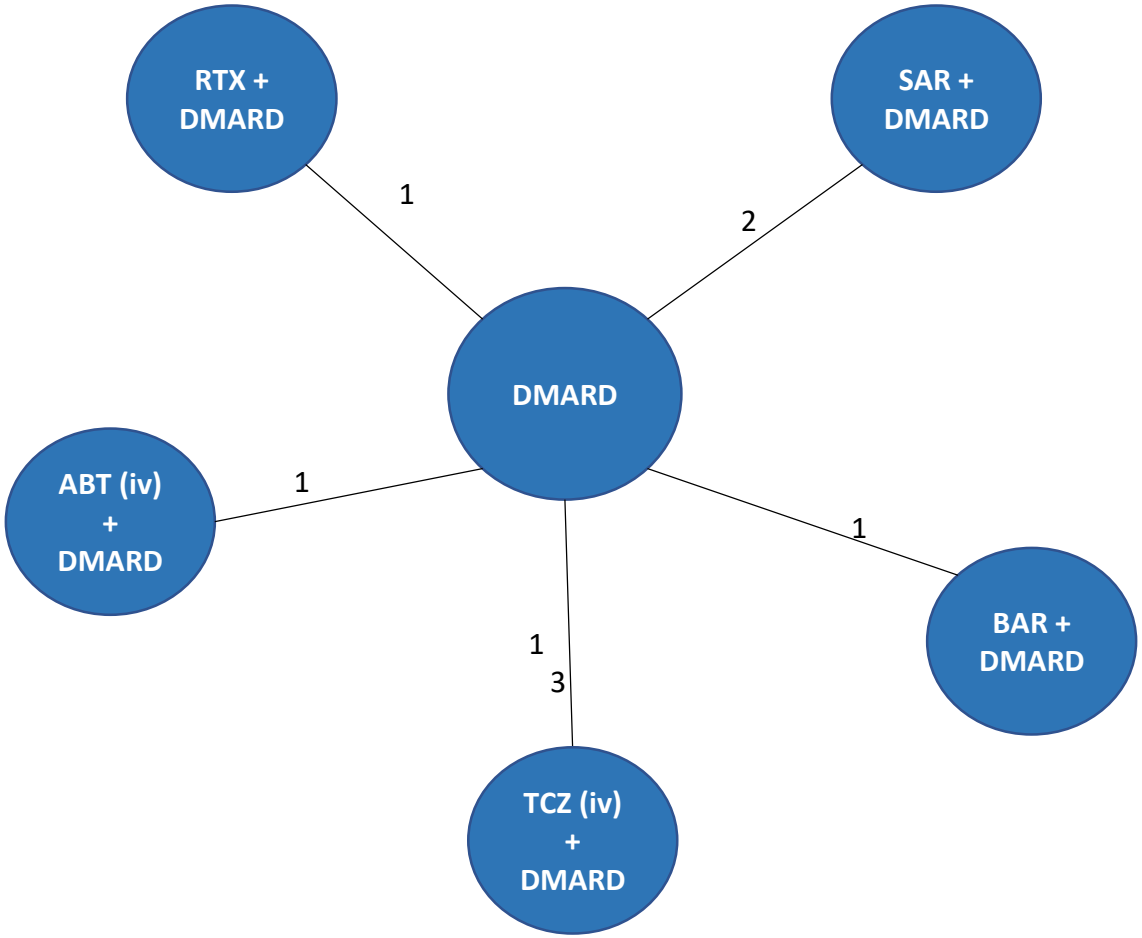
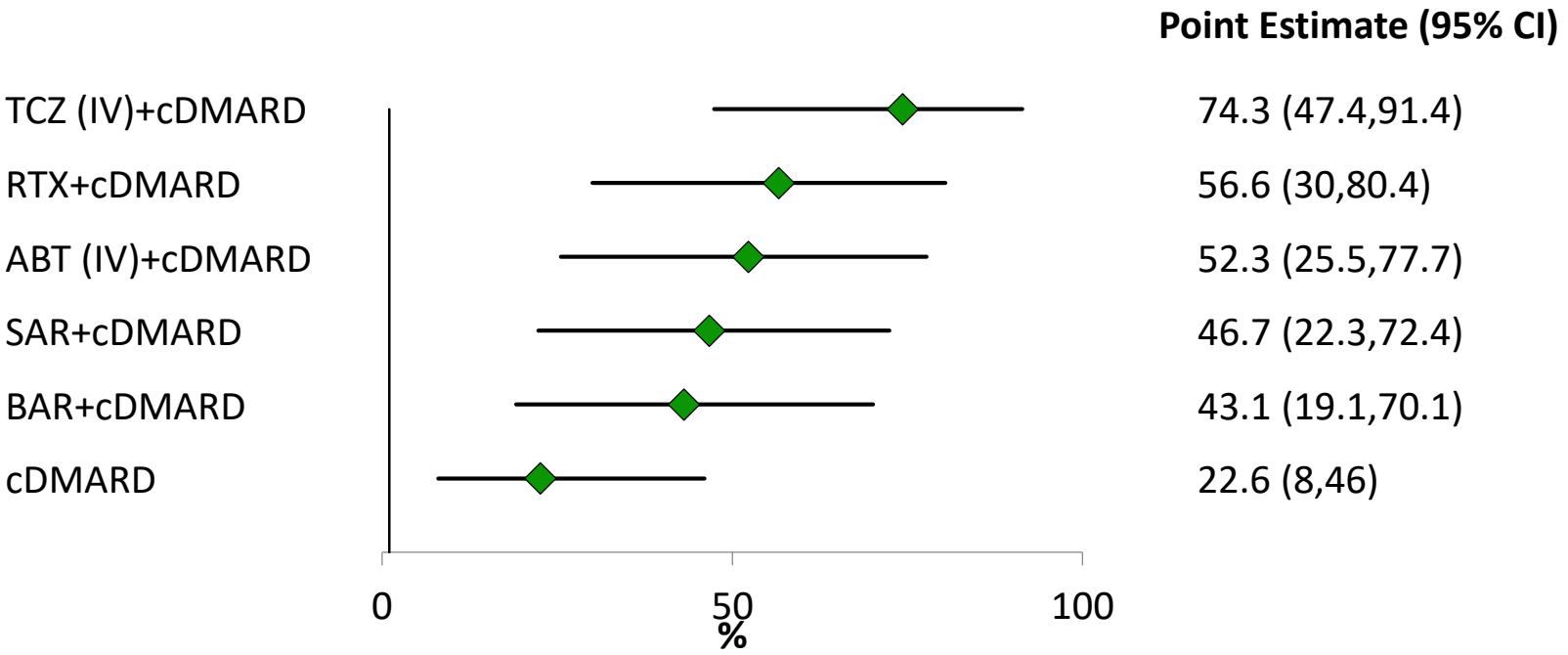
Network Meta-Analysis Derived Proportions of Patients in Each ACR Response Category, by Monotherapy Regimen: Mixed Population

Treatment	ACR <20	ACR 20-50	ACR 50-70	ACR 70-100
Tocilizumab (iv)	25%	24%	21%	30%
Etanercept	27%	24%	20%	28%
Sarilumab	28%	25%	20%	27%
Adalimumab	43%	25%	16%	16%
Conventional DMARD	70%	18%	8%	4%

Network Meta-Analysis: TIM-experienced population



≥ACR20, TIM-experienced Population



Network Meta-Analysis Derived Proportions of Patients in each ACR Response Category, by Regimen: TIM-experienced Population

Treatment	ACR <20	ACR 20-50	ACR 50-70	ACR 70-100
Tocilizumab (iv) + DMARD	38%	24%	19%	19%
Rituximab + DMARD	42%	24%	18%	17%
Abatacept (iv) + DMARD	46%	23%	17%	14%
Sarilumab + DMARD	52%	22%	15%	11%
Baricitinib + DMARD	56%	21%	13%	9%
Conventional DMARD	77%	14%	6%	3%

Long-term Cost Effectiveness

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Appendix Slides

Model Cohort Characteristics (base-case)

Characteristic	Value	Source
Mean age	55 years (range 50 to 60 years old)	Curtis et al., 2010
Female	79% (range 73% to 86%)	Curtis et al., 2010
Caucasian	84%	Curtis et al., 2010
Mean Weight	170 pounds	Frayer et al., 2012 (National Health and Nutrition Examination Survey data)
Baseline HAQ	1.7 (range: 1.37 to 2.03)	Curtis et al., 2010
Baseline mTSS	54 (SD: 64)	Lillegraven et al., 2012

Model Cohort Characteristics for TIM Experienced Population

	Value	Primary Source
Mean age	57 years	Pappas et al, 2014
Female	79.9%	Pappas et al, 2014
Caucasian	83.9%	Pappas et al, 2014
Mean weight	170 lbs.	National Health and Nutrition Examination Survey
Baseline HAQ prior to cDMARD treatment benefit	1.79	Calculation (weighted average from biologic-experienced trials)
Baseline mTSS	93	Barnabe et al, 2012

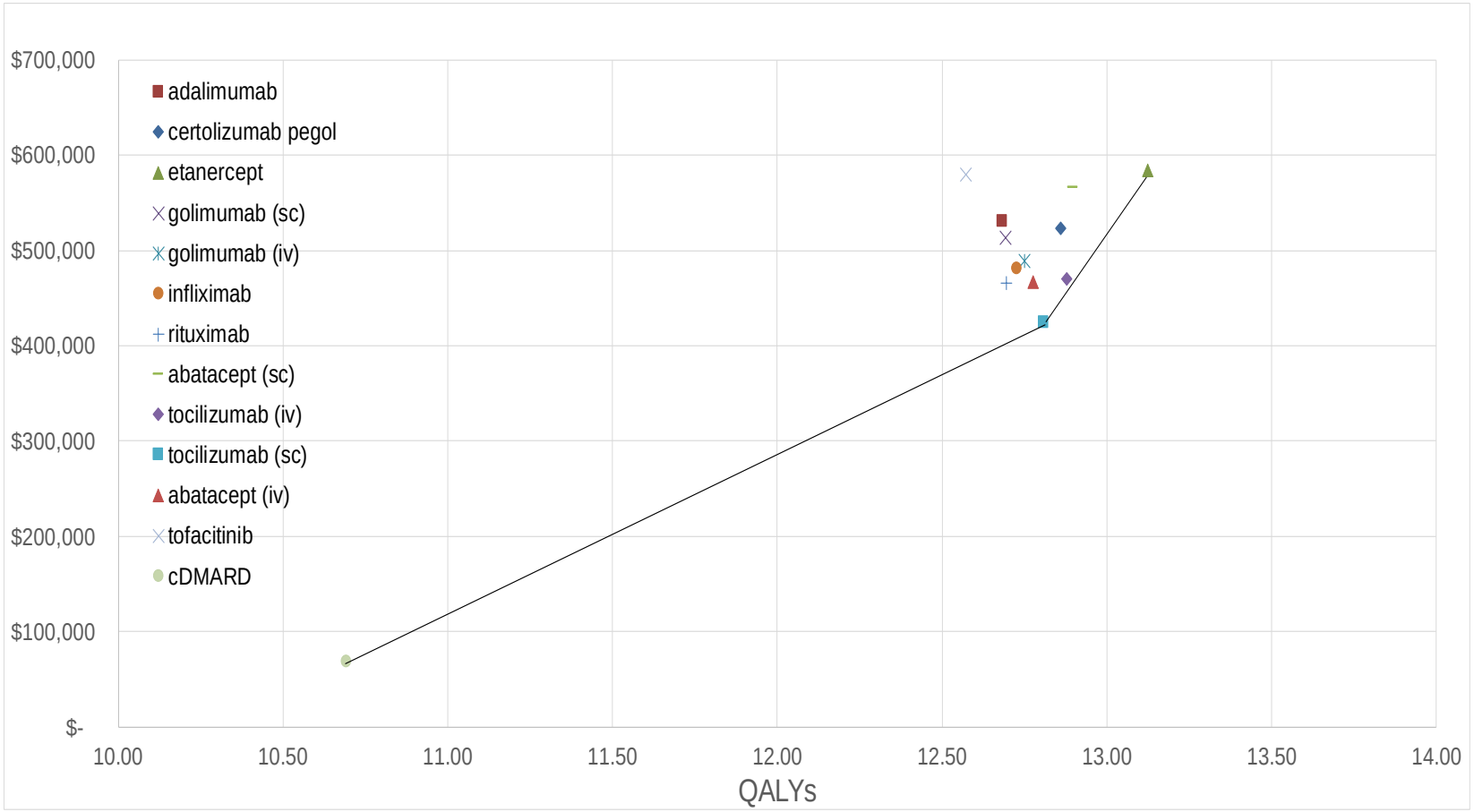
Scenario Analysis Results: TIM Experienced Population versus Mixed Population

	ICER (biologic experienced population)	ICER (mixed population)
rituximab	$196,634	$231,965
abatacept (iv)	$193,664	$220,523
tocilizumab (iv)	$189,370	$213,221

Contributions of ACR and mTSS to HAQ, for TIMs Added on to Conventional DMARD

Treatment 1	Average Proportion of HAQ Contribution from ACR	Average Proportion of HAQ Contribution from mTSS
rituximab	92.1%	7.9%
abatacept (iv)	94.5%	5.5%
abatacept (sc)	92.4%	7.6%
tocilizumab (iv)	91.1%	8.9%
tocilizumab (sc)	91.4%	8.6%
tofacitinib	95.7%	4.3%
adalimumab	93.4%	6.6%
certolizumab pegol	94.6%	5.4%
etanercept	88.9%	11.1%
golimumab (sc)	96.7%	3.3%
golimumab (iv)	93.2%	6.8%
infliximab	89.8%	10.2%

Cost-Effectiveness Frontier for TIMs Added on to Conventional DMARD



Comparisons to the TIM Market Leader; all TIMs added on to Conventional DMARD