
Janus Kinase Inhibitors for Rheumatoid Arthritis: Effectiveness and Value

Public Meeting – December 9, 2019



INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW

Why Are We Here Today?

“In the weeks leading up to my diagnosis of RA, I had so much joint pain and fatigue that I could barely write, buckle my seatbelt, or do laundry. I cycled through countless treatments before I finally found one that worked, but even still, living with this disease will always be a challenge. Though my physical symptoms have improved, I struggle with anxiety and depression, worried about whether I can play with my grandson or if I'll feel well enough to leave the house to see my friends. And for me, the physical pain isn't even the worst part of this disease, but the emotional toll it has on my life and my loved ones.”

- *Patient with RA*

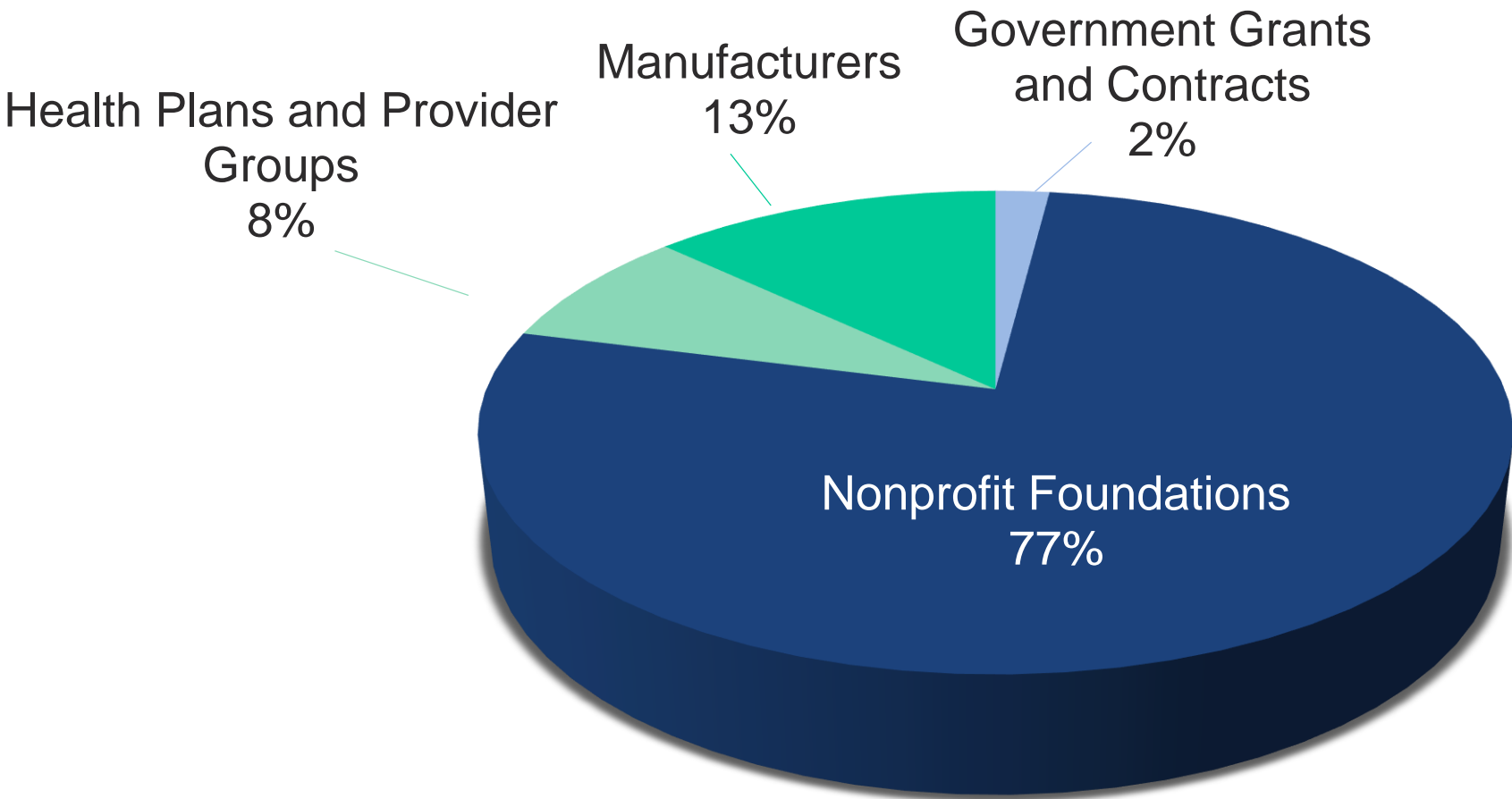
Why Are We Here Today?

- What is happening with innovation, pricing, and coverage policies for autoimmune drugs?
- The goals for today's meeting

Organizational Overview

- California Technology Assessment Forum (CTAF)
- The Institute for Clinical and Economic Review (ICER)

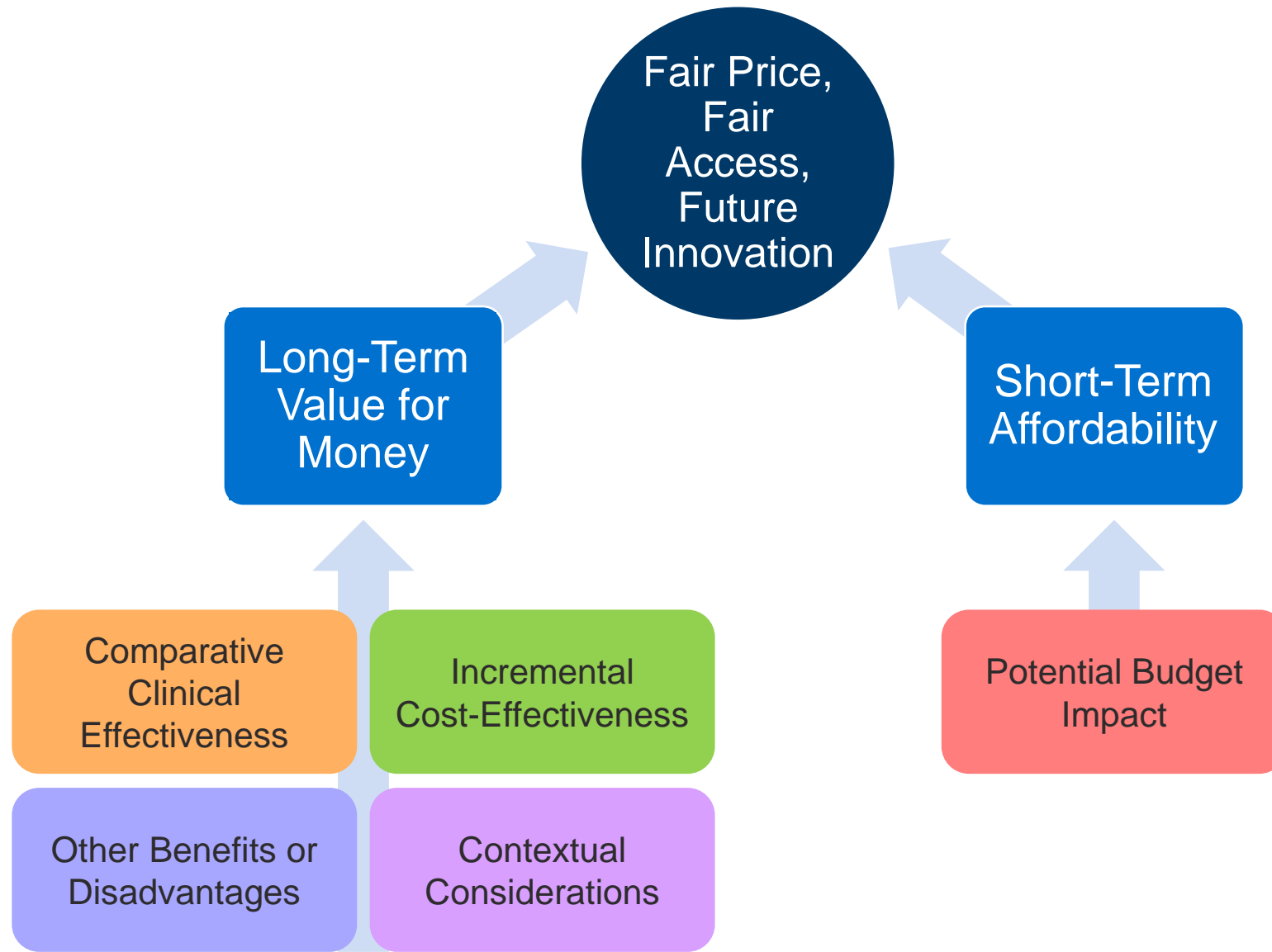
2019 Funding Sources



■ ICER Policy Summit and non-report activities only

How was the ICER report developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Joint ICER/UCSF evidence analysis and internal cost-effectiveness modeling
- Public comment and revision
- Expert reviewers
 - **Andrew L. Concoff, MD, FACR, CAQSM**, Executive Vice President, Chief Value Medical Officer, United Rheumatology
 - **Christopher Phillips, MD**, Chair, American College of Rheumatology Insurance Subcommittee; Rheumatologist, Paducah Rheumatology
 - **Angus B. Worthing, MD, FACP, FACR**, Chair, American College of Rheumatology Committee on Government Affairs
 - **Matthew Stevenson, PhD, BSc**, Professor of Health Technology Assessment, University of Sheffield
- How is the evidence report structured to support CTAF voting and policy discussion?



Agenda

10:00 am	Meeting Convened and Opening Remarks
10:15 am	Presentation of the Evidence
11:15 am	Manufacturer Public Comments and Discussion
11:30 am	Public Comments and Discussion
11:45 am	Lunch
12:45 pm	CTAF Panel Vote
2:00 pm	Break
2:15 pm	Policy Roundtable Discussion
3:30 pm	Reflections from CTAF Panel
4:00 pm	Meeting Adjourned

Clinical Experts

Andrew L. Concoff, MD, FACR, CAQSM, Executive Vice President, Chief Value Medical Officer, United Rheumatology

- *Dr. Concoff has served as a consultant and/or speaker to Flexion Pharmaceuticals, Exagen, Inc., and UCB.*

Christopher Phillips, MD, Chair, American College of Rheumatology Insurance Subcommittee; Rheumatologist, Paducah Rheumatology

- *Dr. Phillips has served as a principal investigator on several upadacitinib trials conducted through an independent multi-specialty clinical research center.*

Patient Experts

Peggy Ehling, Board Chair, Arthritis Foundation Local Leadership Board Los Angeles

- *No conflicts of interest to disclose.*

Julie Eller, Manager of Grassroots Operations, Arthritis Foundation

- *The Arthritis Foundation receives funding from health care companies.*

Evidence Review

Jeffrey A. Tice, MD

Professor of Medicine

University of California, San Francisco



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Key Collaborators

- Noemi Fluetsch, MPH, Research Assistant, ICER
- Serina Herron-Smith, Research Assistant, ICER
- Judith Walsh, MD, MPH, Professor of Medicine, UCSF

Disclosures:

We have no conflicts of interest relevant to this report.

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 (2:1 ratio)
- 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
 - Treat-to-target: 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
- 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

Ongoing Challenges

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

JAK Inhibitors for RA

Class	Drug	Brand Name	Administration
JAK Inhibitors	Upadacitinib	Rinvoq™	Oral
	Tofacitinib	Xeljanz®	Oral
	Baricitinib	Olumiant®	Oral

JAK: Janus kinase

Biosimilar: Infliximab-dyyb (Inflectra®)

- Reference product: infliximab (Remicade®)
 - \$19.9 billion in sales worldwide
 - \$13.7 billion in US
- Indicated for RA, psoriasis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and more
- Example for broader policy discussion of biosimilars in the US

Clinical Evidence

Overview

- **Target population:** patients with moderately-to-severely active RA who experienced inadequate response to previous methotrexate or other cDMARD therapy
- **Interventions:** JAK inhibitors
- **Comparisons of interest:**
 - Head-to-head studies between TIMs (search: only adalimumab)
 - cDMARD therapy alone

Key Outcomes

- Disease activity and remission (DAS28-CRP, DAS28-ESR, 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 health care utilization*
- *Harms*

Evidence Base

- 19 RCTs, three 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

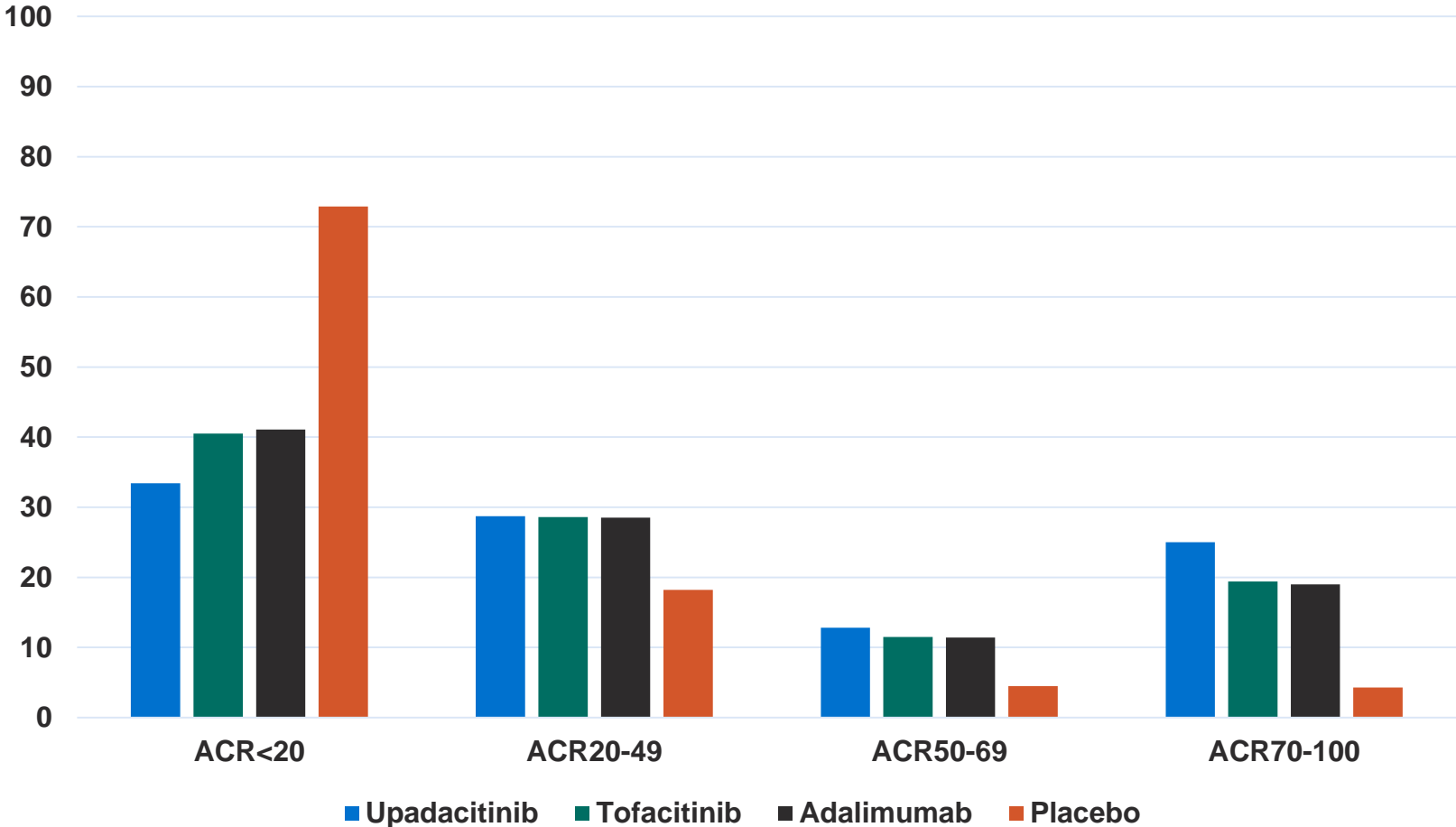
Indirect Comparisons

- Unable to perform NMA for DAS28-CRP/ESR, CDAI, or SDAI
- NMA performed for ACR20/50/70

TIM Naïve/Mixed Population

- Upadacitinib and tofacitinib plus cDMARD versus cDMARD
 - Significant improvements
 - Disease activity, remission, and ACR response added to cDMARD therapy compared to cDMARD therapy alone at 12, 24, and 48 weeks
 - Function and reductions in disability and radiographic progression
 - Quality of life, pain, and fatigue
- Upadacitinib superior to adalimumab in SELECT-COMPARE trial including quality of life, pain, and fatigue
- No data on return to work or school

NMA in TIM-Naïve/Mixed Population: Percentage of Patients in ACR Categories



TIM-Experienced Population

- Upadacitinib, tofacitinib, and baricitinib
 - Significant improvements in disease activity, remission, and ACR response added to cDMARD therapy compared to cDMARD therapy alone at 12, 24, and 48 weeks
 - Significant improvements in function and reductions in disability and radiographic progression
 - Significant improvements in quality of life, fatigue, and pain
 - Few trials, lower N: greater uncertainty compared with TIM-naïve population
 - No outcomes on return to work or school

Harms of JAK inhibitors

- Black box warnings
 - All three: serious infections, lymphoma, testing for latent TB prior to therapy, monitoring for active TB
 - Upadacitinib and baricitinib: thrombosis including DVT, PE, and arterial thrombosis
- Incidence of serious AEs, serious infections, malignancies, and deaths comparable among JAK inhibitors
- 21 RCTs, 11,144 patients: incidence of serious infections low and comparable to placebo
 - 3 per 100 person-years
- Thrombotic events: 0.3 - 0.6 per 100 person years

Controversies & Uncertainties

- Head-to-head data is lacking for JAK inhibitors
- Lack of consistent reporting for disease activity at three months precluded indirect comparisons
- Patients do not feel that current PRO tools sufficiently capture their experience
- Early crossover in DMARD-controlled trials may limit conclusions w/r/t longer-term outcomes
- Long-term effects of prolonged immunomodulation not well-understood for all TIMs

ICER Evidence Ratings

Regimen Type/Comparison	Intervention	Comparator	Rating
TIM-Naïve Population			
Combination Compared to cDMARD	Upadacitinib	cDMARDs	A
	Tofacitinib	cDMARDs	A
	Baricitinib	cDMARDs	I
Head-to-Head	Upadacitinib	Adalimumab	B+
	Tofacitinib	Adalimumab	C
	Baricitinib	Adalimumab	I
TIM-Experienced Population			
Combination with cDMARD	Upadacitinib	cDMARDs	B+
	Tofacitinib	cDMARDs	B+
	Baricitinib	cDMARDs	B+

cDMARD: conventional disease-modifying antirheumatic drug, TIM: targeted immune modulator

Other Benefits and Contextual Considerations

- Rapid return to function and work for patients and their caregivers comparable to other TIMs
- Downstream clinical benefits (e.g., reduced need for disability aids, joint replacement)
- Routes of administration
 - All three JAK inhibitors are oral agents, may be preferable for those with concerns about self-injection or infusion
- RA has a large impact on both length and quality of life

Public Comments Received

- Over-reliance on RCT data to inform evidence base, despite availability of RWE
- Use of DAS28-CRP may bias response rate in favor of JAK inhibitors due to their impact on IL-6
- RA impacts organ systems other than joints (heart, lungs, eyes)

Summary

- Evidence base accumulated over ~20 years documents substantial benefits of TIM therapy over cDMARDs alone
- JAK inhibitors comparable or superior to adalimumab in head-to-head studies
 - Greater uncertainty on long-term safety
- Evidence not adequate to distinguish JAK inhibitor effectiveness or safety

Biosimilars

- Biologics Price Competition and Innovation Act of 2009
 - Increase competition, decrease cost for biologics
 - >20 biosimilars approved by FDA
 - Modest impact on price in US, larger impact in Europe
- Biosimilar must have the same mechanism of action as its reference product (biologic)
- Interchangeability allows substitution without doctor's order
 - Guidance finalized late 2019
 - No biosimilars yet designated as interchangeable

Biosimilar Example: Infliximab-dyyb (Inflectra)

- PLANETRA trial
 - N=606. Primary outcome ACR20 at 30 weeks
 - 60.9% infliximab-dyyb versus 58.6% for infliximab
 - Similar outcomes for ACR50, ACR70, DAS28-ESR, DAS28-CRP, SDAI, CDAI
 - Outcomes at 54 and 102 weeks also similar
 - No differences in adverse events

Questions

Cost-Effectiveness

Rick Chapman, PhD, MS

Director of Health Economics

Institute for Clinical and Economic Review



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Key Review Team Members

- Varun M. Kumar, MBBS, MPH, MSc (Former) Associate Director of Health Economics, ICER

Disclosures:

We have no conflicts of interest relevant to this report.

Objective

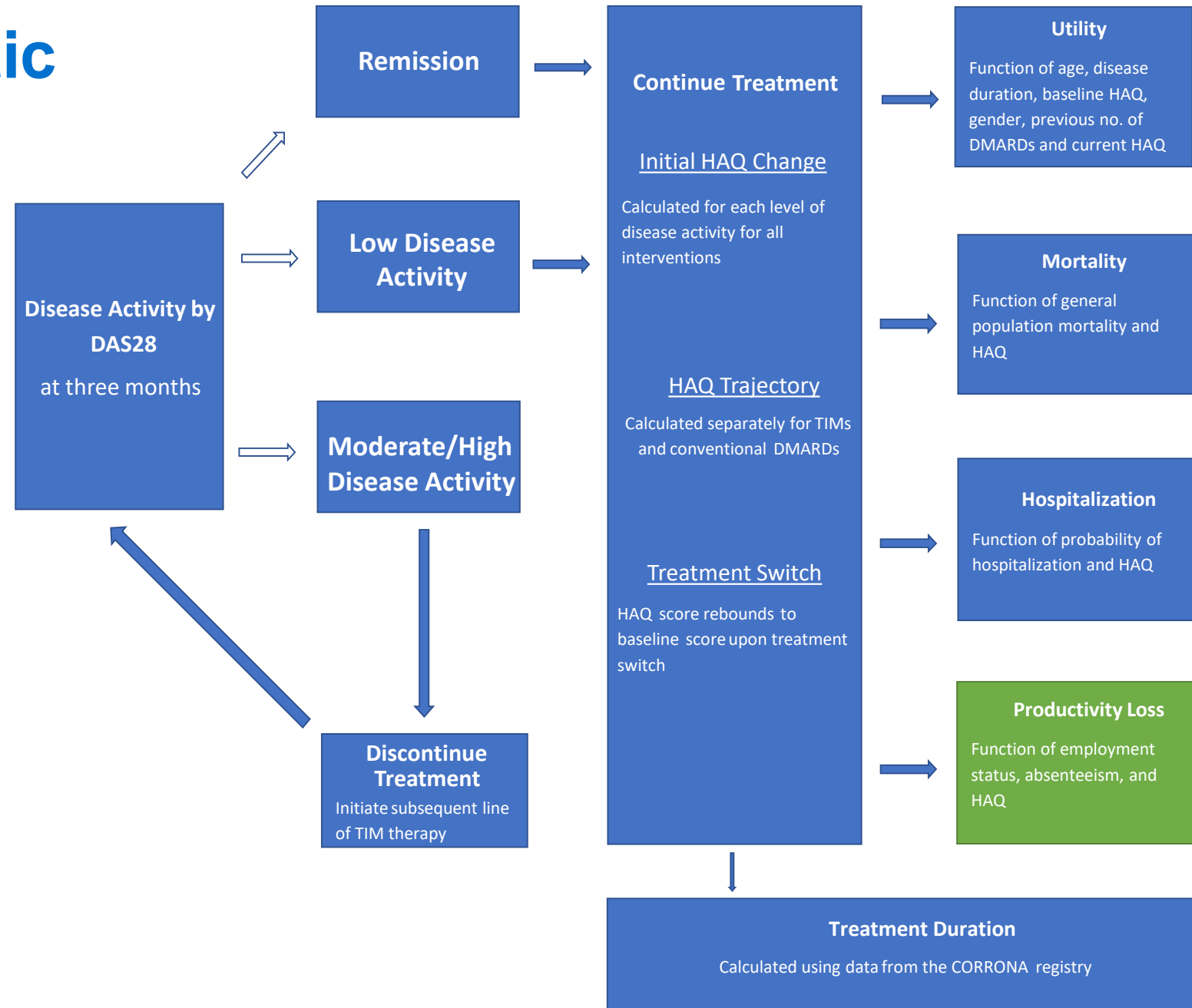
Estimate the cost-effectiveness of upadacitinib + cDMARD therapy versus adalimumab + cDMARD in TIM-naïve patients with moderately-to-severely active RA

Methods in Brief

Methods Overview

- **Model:** *De novo* decision analytic model (results not directly comparable to ICER's 2017 report)
- **Setting:** United States
- **Perspective:** Health care sector perspective
- **Time Horizon:** 1 year
- **Discount Rate:** 3% per year (costs and outcomes)
- **Cycle Length:** 3 months
- **Primary Outcome:** Cost per quality-adjusted life year (QALY) gained
 - Cost per life year (LY) gained and cost per equal value life year gained (evLYG) not relevant over 1-year horizon

Model Schematic



Model Characteristics

- Target population
 - Adults with moderately-to-severely active RA with inadequate response to cDMARDs and naïve to TIM therapy

	Mean Value	Source
Age	54 years	SELECT-COMPARE
Female (%)	79%	
RA Duration	8 years	
Baseline HAQ	1.6	
Baseline DAS28	5.8	

DAS28: Disease Activity Score 28, HAQ: Health Assessment Questionnaire, RA: rheumatoid arthritis

Model Characteristics

- Treatment strategy: upadacitinib plus cDMARD vs. adalimumab plus cDMARD

Key Model Assumptions

- EULAR-to-HAQ mapping algorithm for different DAS28 disease activity categories, assuming remission = “Good” EULAR response, low disease activity = “Moderate,” moderate/high disease activity = “None”
- TIMs for second-line+ market basket were baricitinib, adalimumab, etanercept, tofacitinib, golimumab, and upadacitinib
- Assumed that second-line+ efficacy of market basket of TIM treatment was 84% of calculated average efficacy across included TIMs

Key Model Inputs: Treatment Response at Three Months

	Proportion of Patients Achieving Different Categories of Disease Activity by DAS28 at Three Months*		
	<2.6 (Remission)	2.6 to ≤3.2 (LDA)	>3.2 (MDA and HDA)
Upadacitinib + cDMARD	29%	16%	55%
Adalimumab + cDMARD	18%	11%	71%
2nd-Line Market Basket†	22%	14%	64%

cDMARD: conventional disease-modifying antirheumatic drug, DAS28: Disease Activity Score 28, HDA: high disease activity, LDA: low disease activity, MDA: moderate disease activity, TIM: targeted immune modulator

*Mutually exclusive categories.

†Values prior to applying a 0.84 multiplier to reflect lower efficacy after failure by primary treatment.

Key Model Inputs: Utilities

- Relationship between HAQ and utility based on Wailoo et al.
 - Used health state time-tradeoff evaluations made by US general population sample using EQ-5D
- EQ-5D scores calculated using equation including:
 - Patient age and sex
 - Disease duration
 - # previous DMARDs
 - Baseline HAQ
 - Current HAQ
- Disutility (-0.156) for one month for serious infection

Key Model Inputs: Costs

Drug	Annual WAC	Discount from WAC	Annual Net Price
Upadacitinib 15 mg Tab	\$59,860	26%*	\$44,035
Adalimumab 40 mg/0.8 ml Sol	\$67,263	34%	\$44,102
Methotrexate Sodium 2.5 mg Tab	\$796	--	\$796

mg: milligram, ml: milliliter, tab: tablet, sol: solution, WAC: wholesale acquisition cost

*Discount calculated as the average discount estimated for the other two JAK inhibitors.

Results

Base-Case Results: Upadacitinib vs. Adalimumab

Treatment	Drug Cost* (Line One)	Total Cost	LYs	QALYs	Months in Remission (Line One)
Upadacitinib + cDMARD	\$21,400	\$48,200	0.985	0.699	2.8
Adalimumab + cDMARD	\$15,800	\$47,600	0.985	0.693	1.7
Incremental Cost per...	--	--	--	\$92,000	\$600

cDMARD: conventional disease-modifying antirheumatic drug, evLYG: equal value of life years gained, LY: life year, QALY: quality-adjusted life year
 *Only costs of TIM; does not include cDMARD cost.

Sensitivity Analyses

- One-way
 - For upadacitinib compared to adalimumab, only major driver of results was cost of second-line TIM market basket
- Probabilistic

	Cost-Effective at \$50,000 per QALY	Cost-Effective at \$100,000 per QALY	Cost-Effective at \$150,000 per QALY
Upadacitinib + cDMARD vs. Adalimumab + cDMARD	26%	54%	80%

cDMARD: conventional disease modifying antirheumatic drug, QALY: quality-adjusted life year

Limitations

- Treatment sequencing not standardized, making it difficult to isolate effect of initial TIM therapies over lifetime horizon
- Unable to directly compare upadacitinib and other JAK inhibitors due to lack of published data
- Use of same treatment discontinuation rate for TIMs and cDMARDs due to no robust long-term published data for all treatments
- Disease activity as measured using DAS28 mapped to EULAR response categories, in absence of validated mapping algorithm from DAS28 to HAQ

Comments Received

- Lifetime horizon rather than one year
- DAS28 to EULAR to HAQ-DI crosswalk not validated
- Use DAS28-ESR rather than DAS28-CRP because of JAK inhibitors' impact on DAS28-CRP due to unique mechanism of action
- Provide disclaimer around differences from previous report to reduce the risk of misinterpretation by decision-makers

Conclusions

- Upadacitinib provided marginal clinical benefit over adalimumab at higher cost, resulting in incremental cost-effectiveness ratio falling below commonly-cited thresholds
- More comparable data are required on the short and long-term efficacy of JAK inhibitors and other treatments to allow for direct comparisons among them

Questions

Manufacturer Public Comment and Discussion

Marc Jensen, PharmD

Senior Director, Inflammation and Immunology Field Medical, Pfizer

Conflicts of Interest:

- Employee of Pfizer.

Public Comment and Discussion

Amanda Grimm Wiegrefe, MScHSRA

Director, Regulator Affairs, American College of Rheumatology

Conflicts of Interest:

- No conflicts of interest to disclose.

Lunch

Meeting will resume at 12:45pm

Voting Questions

0. Though today the Marriott is known as a hotel, in 1927 the Marriott was known as what?

- A. A root beer stand
- B. A travel agency
- C. The apartment that housed the Oakland Athletics baseball team
- D. A pharmaceutical company



Patient population for questions 1-6:

Adults ages 18 or older with moderately-to-severely active RA on conventional DMARD therapy who are naïve to TIMs.

1. In patients who are naïve to TIMs, is the evidence adequate to demonstrate that the net health benefit of upadacitinib plus a conventional DMARD is superior to that provided by a conventional DMARD alone?

- A. Yes
- B. No



2. In patients who are naïve to TIMs, is the evidence adequate to demonstrate that the net health benefit of upadacitinib plus a conventional DMARD is superior to that provided by adalimumab plus a conventional DMARD?

- A. Yes
- B. No



3. In patients who are naïve to TIMs, is the evidence adequate to demonstrate that the net health benefit of tofacitinib plus a conventional DMARD is superior to that provided by a conventional DMARD alone?

- A. Yes
- B. No



4. In patients who are naïve to TIMs, is the evidence adequate to demonstrate that the net health benefit of tofacitinib plus a conventional DMARD is superior to that provided by adalimumab plus a conventional DMARD?

- A. Yes
- B. No



5. In patients who are naïve to TIMs, is the evidence adequate to distinguish the net health benefit between upadacitinib and tofacitinib?

- A. Yes
- B. No



5a. If the answer to Q5 is Yes: Based on the available evidence in patients who are naïve to TIMs, which therapy has a greater net health benefit: (a) upadacitinib plus a conventional DMARD, or (b) tofacitinib plus a conventional DMARD?

- A. Upadacitinib
- B. Tofacitinib



6. In patients who are naïve to TIMs, is the evidence adequate to demonstrate that the biosimilar infliximab-dyyb produces a net health benefit comparable to that of the originator biologic infliximab?

- A. Yes
- B. No



Patient population for questions 7-9:

Adults ages 18 or older with moderately-to-severely active RA who are TIM-experienced.

7. In patients who are TIM-experienced, is the evidence adequate to demonstrate that the net health benefit of upadacitinib plus a conventional DMARD is superior to that provided by a conventional DMARD alone?

- A. Yes
- B. No



8. In patients who are TIM-experienced, is the evidence adequate to demonstrate that the net health benefit of tofacitinib plus a conventional DMARD is superior to that provided by a conventional DMARD alone?

- A. Yes
- B. No



9. In patients who are TIM-experienced, is the evidence adequate to demonstrate that the net health benefit of baricitinib plus a conventional DMARD is superior to that provided by a conventional DMARD alone?

- A. Yes
- B. No

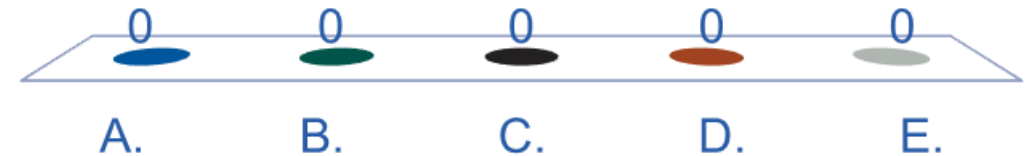


Patient population for questions 10-11:

Adults ages 18 or older with moderately-to-severely active RA who are TIM-naïve and were failed by conventional DMARDs.

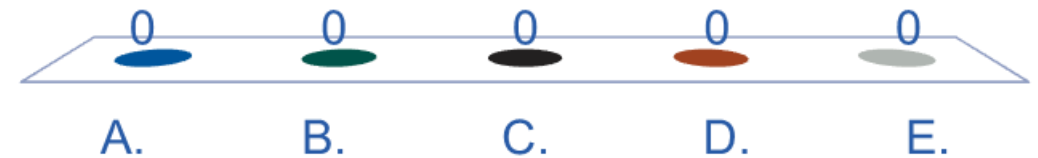
10. Does treating patients with upadacitinib plus a conventional DMARD offer one or more of the following potential “other benefits” in comparison to adalimumab plus a conventional DMARD? (Select all that apply.)

- A. This intervention offers reduced complexity that will significantly improve patient outcomes.
- B. This intervention will significantly reduce caregiver or broader family burden.
- C. This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
- D. This intervention will have a significant impact on improving patients’ ability to return to work and/or their overall productivity.
- E. There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.



11. Are any of the following contextual considerations important in assessing the long-term value for money at current pricing of upadacitinib? (Select all that apply.)

- A. This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
- B. This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
- C. Compared to adalimumab, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
- D. Compared to adalimumab, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
- E. There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

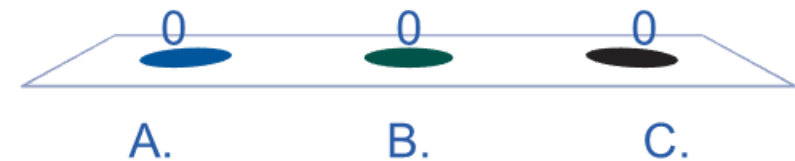


Patient population for question 12:

Adults ages 18 or older with moderately-to-severely active RA who are naïve to TIMs.

12. Given the available evidence on comparative effectiveness, incremental cost-effectiveness using the net price estimate of 26% off the WAC, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with upadacitinib plus a conventional DMARD versus adalimumab plus a conventional DMARD?

- A. Low long-term value for money at estimated pricing
- B. Intermediate long-term value for money at estimated pricing
- C. High long-term value for money at estimated pricing



Break

Meeting will resume at 2:15pm

Policy Roundtable

Policy Roundtable Participants

Participant	Title and Affiliation	Conflict of Interest
Happy Chan, DO, FACR	Medical Director, Medical Care Solutions, Blue Shield of California	Employee of Blue Shield of California.
Andrew L. Concoff, MD, FACR, CAQSM	Executive Vice President, Chief Value Medical Officer, United Rheumatology	Dr. Concoff served as a consultant and/or speaker to Flexion Pharmaceuticals, Exagen, Inc., and UCB.
Peggy Ehling	Board Chair, Arthritis Foundation Local Leadership Board Los Angeles	No conflicts of interest to disclose.
Julie Eller	Manager of Grassroots Advocacy, Arthritis Foundation	The Arthritis Foundation receives funding from health care companies.
Kirstin Griffing, MD, MS, FACR	Senior Medical Advisor, United States Medical Affairs, Rheumatology, Eli Lilly and Company	Employee of Eli Lilly and Company.
Marc Jensen, PharmD	Senior Director, Inflammation and Immunology Field Medical, Pfizer	Employee of Pfizer.
Christopher Phillips, MD	Chair, American College of Rheumatology Insurance Subcommittee; Rheumatologist, Paducah Rheumatology	Dr. Phillips served as a principal investigator on several upadacitinib trials conducted through an independent multi-specialty research center.
John S. Yao, MD, MPH, MBA, MPP, CPC, FACP	Regional Vice President and Chief Medical Officer, Anthem Blue Cross	Employee of Anthem Blue Cross.

CTAF Panel Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on or around January 9, 2020
 - Includes description of CTAF votes, deliberation, policy roundtable discussion
- Materials available at: <https://icer-review.org/topic/arthritis/>

Adjourn