IVI INNOVATION AND VALUE INITIATIVE

Open Source Value Project: RA Model

Public Comments

March 2018

IVI INNOVATION AND VALUE INITIATIVE

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AbbVie

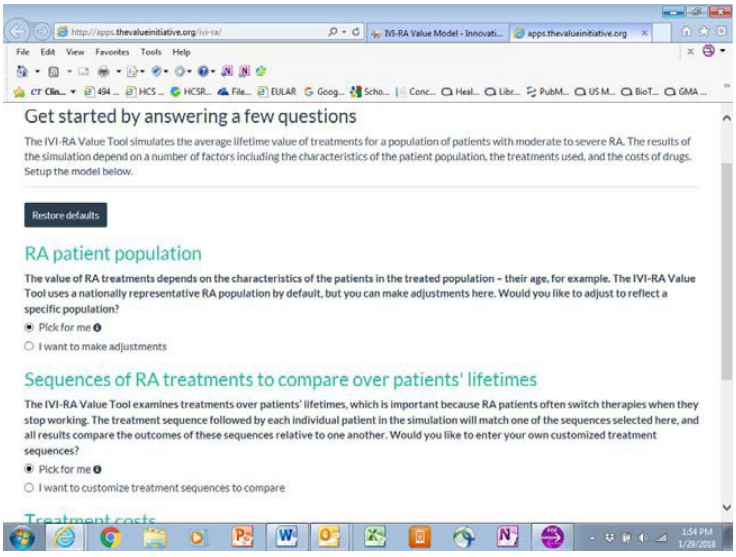
Received via email from Jenny Griffith

Dear IVI,

Thank you for the opportunity to provide additional input into the IVI RA Value Model. As a strategic advisor, we have shared the model internally and have obtained additional feedback for your consideration.

Model Structure

1. The ability to choose one of three possible model structures in the IVI-RA Model Interface allows the user a good deal of freedom, however, it is difficult to identify which of the model structures was used in the IVI-RA Value Tool:
    a. In fact, the IVI-RA Value Tool severely limits the options which previously were available in the IVI-RA Model Interface.
    b. It would be helpful to have an appendix available which lists all of the default options which were selected and what the input values used in the Value Tool were utilized
    c. A footnote explaining the modeling approach used would be very helpful.
2. While the Value Tool allows the user to switch comparator sequences, it is unclear how the default sequence is chosen, and whether it is the most relevant sequence to compare.
    a. A description of this default population would be helpful. Assuming this is high disease activity with average of 3.28 prior csDMARDs. Based on defaults in the tool, appears the biologic sequence is being used first line without prior csDMARDs.
3. When selecting base-case settings for sequencing, the language could be somewhat confusing since it first discusses a lifetime time horizon, then says "….when they stop working." Reader may think the model refers to the patient ending employment rather than the medicine stop working. Also, it is not accurate to imply that everyone's medicine will stop working. We have patients on the same treatment for many years.



4. The model appears to operate with two treatment courses i.e. sequence 1, and sequence 2. It is not intuitively clear what "sequence 1" really is since there's just a descriptor of "cDMARDs". It would be helpful to know if "cDMARDs" is a series of commonly prescribed cDMARDs that are used in some rational order, or if it is just a bucket of cDMARDs.

5. In the sequence 1 vs 2 description, it would be helpful to understand clearly if patients are only included in sequence #2 after they had failed Sequence #1, and if they did have to fail #1 first did they fail just one cDMARD or multiple cDMARDs?

Results:

1. In the clinical economic outcomes from treatment, it would be helpful to have a graph corresponding to total QALYs
2. Unclear how the incremental costs are calculated in the 'Value' tab. For example, the mean total healthcare costs are $56.31k for Sequence 1 and $557.88k for Sequence 2. Based on that graph, one would think the incremental costs would be $501.57k. However, in the 'Value' tab it calculates the incremental costs as $373.61k, it is unclear what accounts for this difference. Might be helpful in the Cost Effectiveness table to add in the actual QALYs and Costs for each sequence.
3. There is a wide variety in the ICER results corresponding to the exact same model inputs. This could be due to a small number of iterations chosen to reduce run-time. Having such a wide variation in ICER results could result in "cherry-picking" where users run the model multiple times and then report the set of results they find most favorable.
4. The default Willingness to pay per QALY of $150,000 seems arbitrary and very high, and there are no references to support this figure. The base case result would only be considered cost-effective using such high Willingness to pay per QALY, and thus the results may be misleading.
5. The MCDA piece is an interesting wrinkle. The weights themselves are reasonably intuitive, however, how the actual MCDA values are actually calculated are somewhat opaque.
    a. Would be helpful to provide additional details on how the weights for this base case scenario were established. Is this based on patient-focused research?

American College of Rheumatology

Received via email from Harry Gewanter

Hi there!

I like your model very much as it provides more depth and substance to the decision-making process by incorporating factors other than just money. I do have a number of suggestions/comments.

- I realize this is a near-impossible task, but the problem with this (and all other models) is that what you consider "cost" is really "list-price". Nobody knows what the real costs are given the lack of transparency within the the health-care systems. We may know AWP, but we do not know the discounts, rebates, other fees and monetary shenanigans utilized by insurers, pharmacy benefit managers, pharmaceutical manufacturers or distributors that constitute the true costs. Further, very few physicians can tell you how much it "costs" to see an individual patient. I understand this is a systemic problem and therefore your model is comparable with, say, ICER as y'all are presumably using the same data, but I think you may want to put in a disclaimer about what is truly being evaluated.

- There are a number of areas where I think you can improve the explanations of your findings.
  - How much change in the HAQ is significant? What is the context for the numbers (ie, what does a "2" mean)?
  - Adding a ruler or better measurement benchmarks to the Life Expectancy (and other) graphs would make them more meaningful and understandable. In your standard example, I couldn't suss out how much difference was present.
  - I think it would be helpful to include "denominators"and better/clearer descriptors for your various findings. For example, are the Healthcare Costs listed per year, per lifetime, per decade, etc? Are these for the individual or the population? The same can be said for the Days in Hospital, Earnings, Number of Infections, etc.

- While your glossary is helpful, it needs to be made into more readable English and less "Economic-Ese". Having specific explanations and examples for non-economists would make this project more user-friendly, understandable and acceptable. Along the same line, since much of the model is based on QALYs and "Willingness to Pay" criteria, more robust explanations of these terms are necessary.

- Where did the $150K/QALY come from? Knowing the source would make it more believable as a baseline figure.

- Within your MCDA page, the slider scales are not intuitive and I was not sure how to interpret what it meant when I moved the slider to the left or the right. Are these integral scales, logarithmic or something else? Again, more context is necessary to make this valuable aspect of the model more useful and practical.

- I think it would be helpful to try to identify additional patient preference issues and add them to the model. For example, does the age of the patient matter? What about an upcoming significant event, such as the birth of a grandchild? We know those issues change one's "value system" regarding health care choice; I don't know how to include them in the model, but I don't see a place for these critical aspects of decision-making.

- I realize these are extraordinarily difficult components to include, but consideration of which joints are involved (ie, hands vs hips vs knees vs jaws, etc) and the impact of surgery on the disease, productivity, etc would make the model even more "realistic". Similarly, there are a number of "extra-articular" issues that go along with RA beyond infections (ie, uveitis, rheumatoid lung, etc) as well as "extra-articular" benefits of treatment (ie, decreased cardiovascular disease) that could be added into the model as they are confounders.

- I loved having the productivity measure within the model. Treating RA is not just a "debit" of the treatment costs, it is also a "debit" of loss of income and community participation. However, along this thread, it might be helpful to add a similar "family" community slider (if that is possible) since someone with RA may result in additional family/community care taking costs, both direct and indirect and these are not small amounts.

- I liked the concept of what it meant to have RA if you are healthy. Not something usually considered.

- I don't know how hard it would be to add more options to the "Not entirely average" modifier (ie, quintiles, etc) to allow additional explorations of response.

I hope these thoughts are helpful. Keep up the good work and keep improving the model.

Harry L. Gewanter, MD, FAAP, MACR

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Chair, RheumPAC, American College of Rheumatology
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Arthritis Foundation

Received via email from Suzanne Schrandt

Hi Jennifer,

I actually was able to connect with Guy tonight and he had similar thoughts to mine, so I'm sharing our feedback here.

The tool is somewhat difficult to use/understand and, depending on the specific function/parameter can be either too complex or too simple. That said, it seems like it could have potential, particularly if it was nimble enough to be used in real time (i.e., imagine a hill briefing where a PAO can show the longitudinal cost effectiveness of a public health program paying for a specific category of drugs). One key challenge is that the tool is incredibly complicated (in its current form) for a patient or PAO to use, or perhaps anyone who isn't an HEOR expert, but it seems too simple for an actual HEOR expert to be using (or someone on the "inside' of a health plan/insurer who would be relying on their own actuaries. Might it be necessary to further customize the tool depending on the intended end-user?

Specific comments:

- The purpose of the tool as stated is confusing/concerning; on the opening frame there is no mention of identifying treatments (even at a population level) that are likely to have the best treatment effect. Rather, the only stated goal relates to allocating healthcare dollars. It seems like the portion of the equation dedicated to working to improve health outcomes for patients should be given some above-the-fold space?
- It is great that two patient focus groups were conducted but that doesn't seem to be a robust enough patient engagement approach. What was the role of the patients on the steering committee and can you share any examples of the types of insights patients shared that actually shaped the tool? A more robust, iterative patient engagement approach would likely be fruitful—one that begins at the very earliest stages of conceptualizing a disease-specific value tool.
- The treatment sequence information is difficult to follow; is the suggestion that all of these drugs were used? For how long? What was the impetus for d/c and beginning a new one? Was there a lag time between treatments due to access challenges (step therapy, prior auth., etc.)?
- The time parameter/amount of fluctuation that occurs but is not captured or visualized in the "Change of patient functional status" bars is confusing. It is nice to see in vivid color the significant difference between HAQ scores in DMARD-only treatment vs. biologic treatments, but with such a volatile disease, seeing a static representation of what happens over a lifetime seems incomplete.
- Do the underlying assumptions in the model fully represent the patient population?
- Is there really enough data to know impact of biologics on life expectancy? People have only had access to them since 2000; are you including people who were diagnosed prior to that and treated with non-biological DMARD cocktails first, and then switched to biologics? If so, that may need to be teased out/explained.
- Given that this is an RA tool, why wasn't RAPID-3 used?
- What is the reasoning for the "value to the currently healthy" element of the model? It seems like this would be more relevant in contagious diseases?
- QALYs have pretty significant limitations from a disease/disability perspective and don't offer a full, humanized perspective of the real experience of RA. In the absence of another measure to use, it makes sense that QALYs were used, but as new options emerge, they should be taken into consideration.

I know it will be past the due date, but my Patient Leadership Council (ten-member patient advisory body at the Arthritis Foundation) has an in-person meeting on March 11th and I'd like to present he tool and get their feedback on it there. Happy to share that feedback with you if it is not too late.

Many thanks,
Suz

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January 17, 2018

Darius Lakdawalla & Jason Shafrin
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research@thevalueinitiative.org

BY ELECTRONIC DELIVERY

Re: Proposed IVI-RA Model

Dear Dr. Lakdawalla and Dr. Shafrin:

As a leader in immunology research, Bristol-Myers Squibb (BMS) acknowledges the importance of understanding and fully characterizing the value that innovative therapies provide to patients, and appreciates the opportunity to comment on the Innovation and Value Initiative (IVI) Rheumatoid Arthritis (RA) Model as part of IVI's Open Source Value Project (OSVP). BMS is dedicated to advancing the science of immunology and to disseminating the results of our research to ensure that our work can benefit the widest range of patients.

We have reviewed the current version of the IVI-RA model and believe it could benefit from the following feedback to guide its ongoing development.

Refine with HLC's Principles of Value Frameworks

BMS agrees with IVI's patient centric and transparent approach to developing the current version of the IVI-RA model. For example, the patient focus groups conducted initially were a key resource in developing the model. As IVI looks to refine the RA model further, we recommend referring to a set of principles on value frameworks developed by the Healthcare Leadership Council (HLC), a coalition of chief executives from all disciplines within American healthcare. In 2017, HLC released the following set of principles that should guide the creation of value frameworks being used to determine the cost-effectiveness of new healthcare innovations[i]. These align also with our own company's principles on value frameworks.

1. Collect patient and provider input on what "value" should be measured in a treatment option in order to measure outcomes that matter to patients and providers (such subjective data as discomfort during or after treatment).
2. A diverse group of disease area experts should participate in both the development of methodology and assessments before these are submitted through a peer review process to ensure scientific rigor.
3. During and after the review process, provide full transparency of evaluation criteria, including any models and data used – allowing for research to be analyzed and results replicated by others.

4. Assess and reassess value over time (recognizing that prices can vary over time), to capture appropriately the value of curative or preventative treatments whose full value may not be realized until after the initial approval.
5. Define value to society broadly – this includes outcomes values such as productivity, opportunity costs, and avoided long-term costs.
6. Incorporate real-world evidence and adjust evaluation techniques to capture actual patient outcomes and preference for treatment, recognizing some data may be difficult to obtain for pragmatic or ethical reasons.
7. Treatments should accurately reflect real-world usage.
8. Consider variations in treatment setting, technique, and provider when evaluating a new product or technique.

Already with the beta version of the RA model, IVI has adhered to many of these principles. As IVI seeks to refine the model, we recommend robust patient and provider engagement, as well as increasing the incorporation of real world evidence. With respect to capturing patient value, we recommend referring to perspectives from the advocacy community in a recent publication in Health Expectations for guidance on additional IVI engagement with patients and patient groups.[ii]

Expand the Model to More Fully Capture All Elements of Value Rather than a Focus on Quality-Adjusted Life-Years (QALYs)

We are encouraged IVI has incorporated other value elements other than the QALY; however, the beta version of IVI-RA proposes the primary health outcome is the QALY. Experts have identified other value elements and BMS believes rather than promulgating the use of this limited measure, value frameworks should aim to incorporate as many elements of value as possible. For example, ISPOR's Special Task Force (STF) on Value Assessment Frameworks has identified twelve different components of value in their draft whitepaper – including QALY, net costs, productivity, adherence improving factors, reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spillovers. This catalogue of elements provides one of the first, truly forward-looking steps in comprehensively characterizing all of the multidimensional facets of value. We recommend prioritizing the incorporation of additional value elements into the IVI-RA model in the revision process. While we appreciate that not all of these value elements can be incorporated in every model, as appropriate to the disease state they could further help estimate value. Not only will this help advance the methodology for the value elements identified by ISPOR's STF, but it will more fully capture value to patients and society.

Expand the Role of Safety in the Model and Differentiate Safety Outcomes

In addition to inadequate efficacy, lack of safety in the form of adverse events is also a common reason for RA patients switching medications. The model's primary focus is on patients who switch or discontinue their medication due to efficacy only. This presents a bias toward products with a better efficacy profile and worse safety profile. The model allows switch due to adverse events, but only in the case of serious infection, as these "have a significant cost impact and increased risk over background rates to be meaningful to include." Additional

adverse events are important to patients and result in treatment switching. Therefore, the model should expand beyond serious infections and include other adverse events.

The model also assumes that the infection rate is equal among targeted disease-modifying antirheumatic drugs (tDMARDs) because "the published results for specific tDMARDs are estimated with very little precision." Evidence shows that specific tDMARDs have decreased infection risk compared to other tDMARDs. In RA patients with prior exposure to a biologic agent, exposure to etanercept, infliximab, or rituximab was associated with a greater 1-year risk of hospitalized infection compared to the risk associated with exposure to abatacept.[iii] Among RA patients who experienced a hospitalized infection while on anti-TNF therapy, abatacept and etanercept were associated with the lowest risk of subsequent infection compared to other biologic therapies.[iv] The expected costs of serious infections were lower for IV and SC abatacept than for infliximab and adalimumab in hypothetical analyses based on two large clinical trials.[v] Therefore, the assumption of equal infection rates negatively impacts the performance of these tDMARDs in the model. The model should differentiate rates of serious infection among tDMARDs.

Allow for Analysis Based on Poor Prognostic Factors

Although this model allows more patient heterogeneity than previous cost-effectiveness models, there is still no way to analyze subgroups, such as those with poor prognostic factors and more severe disease. Even if this data is not available across every clinical trial in the network meta-analysis (NMA), the final tool should allow the user to conduct a scenario analysis for different subgroups.

Select the Most Appropriate Outcomes

The model relies on each agent's impact on Heath Assessment Questionnaire (HAQ) Disability Index score during the initial treatment phase and incorporates parameters such as progression defined by HAQ over time, mortality rates as a function of HAQ-based progression, quality of life based on HAQ, and cost based on HAQ-progression. Focusing on this efficacy measure during the initial treatment phase, and no other outcomes, is a limitation. The model should seek out ways to incorporate other measures such as Disease Activity Score (DAS) and American College of Rheumatology (ACR) response (ACR20, ACR50, ACR70, ACR90) to define model outcomes, even if evidence is not as robust as that for HAQ.

Adjustments for HAQ progression for sequencing of patients

BMS would like to bring to IVI's attention that the reference Wolfe and Michaud (2010) for the model's HAQ progression does not take into account the patients' treatment history.[vi] Specifically, a subgroup of patients have been shown to benefit from a TNF to non-TNF sequence compared to TNF cycling.[vii]

Bristol-Myers Squibb appreciates IVI's efforts to engage stakeholders in the development of the IVI-RA model and we look forward to providing continued input to IVI as it refines the model. We welcome the opportunity to meet to further discuss our feedback. If you have any questions, please do not hesitate to contact Michael Ryan, PharmD, Head of U.S. Value, Access &

U.S. Pharmaceuticals
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Payment at (609)302-3198 and Mitch Higashi, PhD, Head of U.S. Health Economics Outcomes Research at (609)302-3798.

Sincerely,

Michael Ryan, PharmD Head of U.S. Value, Access & Payment	Mitch Higashi, PhD Head of U.S. Health Economics & Outcomes Research

References:

[i] Healthcare Leadership Council. Principles on Value Assessment Frameworks. Available at: https://www.hlc.org/app/uploads/2017/05/HLC-Final-Principles-on-Value-Frameworks.pdf

[ii] Addario BJ, Fadich A, Fox J et al. Patient value: perspectives from the advocacy community. Health Expectations. 2017;1-7. Bristol-Myers Squibb provided funding to support the writing and editing of this paper and provided a grant to ensure the paper was published with Open Access.

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[iv] Yun H, Xie F, Delzell E, Chen L, Levitan EB, Lewis JD, Saag KG, Beukelman T, Winthrop K, Baddley JW, Curtis JR. Risk of hospitalized infection in rheumatoid arthritis patients receiving biologics following a previous infection while on treatment with anti-TNF therapy. Ann Rheum Dis 2015, 74(6):1065-71.

[v] S Johnston, S Kelly, A Nadkarni, KL Wilson, B Limone, M Hochberg. Healthcare Costs Associated with Serious Infections Among Biologic-Naïve Rheumatoid Arthritis Patients Initiating First-Line Biologic Treatment. ACR/ARHP Annual Scientific Meeting, November 14-19, 2014, Boston, MA.

[vi] Wolfe F, Michaud K. The loss of health status in rheumatoid arthritis and the effect of biologic therapy: a longitudinal observational study. Arthritis Research & Therapy 2010, 12:R35.

[vii] Gottenberg J-E, Olivier B, Perdriger A et al. Non-TNF-Targeted Biologic vs a Second Anti-TNF Drug to Treat Rheumatoid Arthritis in Patients with Insufficient Response to a First Anti-TNF Drug: A Randomized Clinical Trial. JAMA 2016, 316(11):1172-1180.

Bristol-Myers Squibb

Received via email from Alexander Marshall

Hi Jason and Devin,

Thank you for taking the time to speak with us today on the model. Here is the citation for the AMPLE article we discussed. We also wanted to follow up on key points from the meeting and next steps.

Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis. 2014 Jan;73(1):86-94.

Since the package insert states the abatacept IV loading dose is optional and the pivotal head to head RCT AMPLE does not include an IV loading dose:

• We agree with the suggestion to have the default option for abatacept SC without an IV loading dose.

• When the option to include a loading dose is chosen by the user, it should include a reduced infusion cost. Currently, the infusion cost is the same between abatacept IV and abatacept SC. It should be lower for the SC formulation as there is only one infusion associated with this regimen.

For next steps regarding medications that are available in both IV and SC formulations (Orencia, Actemra, and Simponi):

• Please let us know whether the SC or IV form of golimumab and tocilizumab are currently being used in the model.

• We believe the model should be transparent as to the formulations used for all drugs. Therefore, we recommend all drugs are labeled by their formulation and that all formulations currently available for RA are included in the model.

Thank you again and we look forward to hearing from you!

Best Regards,

Alex and the BMS Team

Genentech
A Member of the Roche Group

February 16, 2018

Innovation and Value Initiative
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RE: Public Comment on the Open Source Development of the IVI-RA Model

Dear IVI-RA Technical Expert Panel:

Genentech, a member of the Roche Group, appreciates the opportunity to provide comments on the Innovation and Value Initiative's (IVI) rheumatoid arthritis (RA) model. We commend IVI's efforts in facilitating an open source, transparent process for estimating the value of health care technologies for a broad set of stakeholders.

Genentech is committed to advancing the scientific understanding of RA and pursuing the development of novel therapies to help individuals diagnosed with this chronic and debilitating disease. Treatment decisions for patients with RA are complex and personal. We support initiatives that account for the needs of individual patients and facilitate a meaningful dialogue between a broad set of stakeholders.

Our comments are focused on enhancing IVI-RA model's usability for a diverse set of users and clarifying model assumptions. We hope our recommendations contribute to improving the IVI-RA model and advancing the field of value assessment.

IVI-RA Value Tool

Additional enhancements to the model will increase the end user's ability to customize it to meet their individual needs and obtain information most relevant to their decision making. For those unfamiliar with the complexity of the RA disease landscape, the numerous customization options risk confusion. Additional context and guidance will better equip users in navigating the model and obtain meaningful analyses. Genentech recommends the following:

1. Avoid potentially biasing the user by removing the default sequence in the Setup function of the model. The model default currently compares a sequence of six "targeted" DMARDs to conventional DMARDs alone. Multiple, alternative treatment sequences are

consistent with ACR guidelines and real-world practice due to the heterogeneity and complexity of RA. The ACR guidelines recommend that patients with established RA who fail DMARD monotherapy move to combination DMARD therapy, add a necrosis factor inhibitor (TNFi) with or without methotrexate (MTX) or add a non-TNFi biologic with or without MTX, in no particular order of preference.[1] The guidelines also conditionally recommend using a non-TNFi or a TNFi after TNFi failure. The default sequence currently in the model begins with two TNFis in combination with MTX, i.e., adalimumab followed by etanercept. However, clinical evidence supports switching to a non-TNFi after first TNFi failure. [2,3] Therefore, since many alternative options consistent with ACR guidelines are available, we recommend removing the default sequence, and allow users to choose their own sequence.

2. Mitigate potential misinterpretation of health care costs presented in the Outcomes function by clarifying that the costs represent those incurred over the lifetime model time horizon, which include costs after completing treatment(s) specified in model comparators.
3. Enable greater customization to user perspective by including the ability to modify the model time horizon since preferred time horizons will vary based on user perspective.
4. Facilitate ease of use of the model by describing source data that informs the clinical and economic outcomes for each treatment option in the Outcomes function.
5. Guide users to a more accurate interpretation of the Health Assessment Questionnaire (HAQ) Disability Index results, an important measure of patients' health status in RA, by including alternative means of presenting the change in functional status, such as "better" and "worse" on the y-axis.

IVI-RA Model Interface

The IVI-RA Model Interface is provided as an option for users who want increased control over model parameters and structural assumptions. We appreciate IVI for developing a highly flexible model. To increase ease of use for those seeking greater customization of the IVI-RA model, we recommend the following:

1. Guide users with pertinent details upfront in the introduction in order to avoid confusion. For example, we recommend providing a diagram to detail the IVI-RA model is a discrete-time individual patient simulation that simulates outcomes for individual patients.
2. Provide additional background and implications around the selection of the HAQ, ACR and DAS28 in respect to treatment and treatment switch.

3. Enable users to have a sound understanding of their starting point by outlining the rationale for base case assumptions in the Model Interface. For example, it is not readily apparent why a generalized gamma distribution for treatment duration was chosen.
4. Comprehensively account for uncertainty by including a deterministic sensitivity analysis and complementing the existing probabilistic sensitivity analysis.

Multi-Criteria Decision Analysis (MCDA)

We commend IVI for incorporating MCDA into IVI-RA given traditional measures of value, such as cost-effectiveness analyses, may not adequately capture value for all health care stakeholders. It is important that treatment attributes most valuable to patients are integrated into health care decision making. As stated by IVI, we agree that factors such as patient out-of-pocket costs and side effect profiles should be included in the MCDA framework and highlights an important next step for IVI-RA. In addition, we recommend providing background information to how best to interpret the MCDA with direct links to the technical report and additional information boxes. Furthermore, clarification around how MCDA parameters were placed on a common scale and the rationale for default settings will help uers navigate and customize the MCDA to meet their needs.

Additional Recommendations

We recommend the following corrections and modifications to accurately reflect current available treatment options in RA.

1. Tocilizumab monotherapy, in subcutaneous (SC) and intravenous (IV) formulations, should be included as treatment options based on its FDA approved indication[4]. It is important to include both SC and IV formulations given the importance of treatment administration in the MCDA.
2. Treatment costs (Set-Up function) should account for different dosing and administration options available for tocilizumab, which includes SC weekly and IV[4]. Currently the IVI model specifies every other week only.
3. Biologic DMARDs should be consistently referred as "bDMARDs" in order to avoid potential confusion with tDMARDs. tDMARDS is sometimes used to denote traditional DMARDs.
4. Rituximab dosing should be consistent with prescribing information. Rituximab IV dosing after two initial infusions is every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks[5]. Note that rituximab monotherapy is considered off-label as it is FDA-approved to be used in combination with MTX.

Genentech offers IVI our support and partnership given our long standing position in RA and desire to advance the field of value assessment. We hope that IVI finds our comments helpful in the next iteration of the IVI-RA and achieving a transparent process for estimating the value of health care technologies for diverse health care stakeholders.

Sincerely,

Jan Hansen, PhD
Vice President, Evidence for Access
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References:

1. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016 Jan;68(1):125. https://www.rheumatology.org/Portals/0/Files/ACR%202015%20RA%20Guideline.pdf
2. Gottenberg JE, Brocq O, Perdriger A, et al. Non-TNF-targeted biologic vs a second anti-TNF drug to treat rheumatoid arthritis in patients with insufficient response to a first anti-TNF drug: A randomized clinical trial. JAMA. 2016 Sep 20;316(11):1172-1180. https://www.ncbi.nlm.nih.gov/pubmed/27654603
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4. Actemra (tocilizumab) [Package Insert]. Genentech Inc.; South San Francisco, CA; 2017. https://www.gene.com/download/pdf/actemra_prescribing.pdf
5. Rituxan (rituximab) [Package Insert]. Genentech Inc.; South San Francisco, CA; 2015. https://www.gene.com/download/pdf/rituxan_prescribing.pdf

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January 17th, 2018

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Dear IVI-RA modeling team,

Thank you for the opportunity to provide feedback on the RA-IVI model. A team at the Institute for Clinical and Economic Review (ICER) has reviewed the model methodologies, R source code and online model interface. Please find below our comments, suggested revisions, and associated references for your consideration.

Sincerely,

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www.icer-review.org

Major

1. Formulate treatment switching rules (S1-S6) as part of the decision rather than an uncertainty. In section 2.4, one stated use of the model is for evaluating consequences of clinical guidelines. For example, users can (in theory) examine different treatment switching decision rules. However, in the current model setup, treatment switching is considered a "structural uncertainty" rather than a decision or strategy in S1-S6 (although it is symbolized as a decision in Figure 3). It is also unclear why the choice for modeling changes in HAQ scores (H1-H3) limits the available switching strategies. For example, why does modeling HAQ directly preclude treatment switching based on ACR? This limitation has implications throughout the document and the model.

2. Elaborate on the reasons for the differences in results when using the different approaches for modeling HAQ in the initial treatment phase (H1-H3). Were any parameters calibrated to match known scenarios? The data for ACR to EULAR were based on US veterans, which may not be representative of the overall RA population in the US. The other studies similarly may not be representative of the target population.

3. Elaborate on justification for using observational data by Wolfe and Michaud 2010 for deriving annual HAQ change in the 'constant linear rate of progression' approach. ICER recommends using the National Data Bank (NDB) for Rheumatic Diseases dataset in NICE DSU 2015 (Progression of Disease in People with Rheumatoid Arthritis Treated with Non Biologic Therapies), which more closely resembles the model's target population based on gender and age, although HAQ scores in both datasets are similar.[1] The mean annual HAQ change reported in the NICE DSU for the NDB population is 0.0269 while the RA IVI model uses a 0.031 annual HAQ change. While the Michaud et al. 2011 study that IVI has used provides HAQ by age group as well as HAQ based on duration of disease, it does not state duration of disease by age group. The linear relationship of HAQ change over time is not known beyond length of registry follow-up data, about 15 years on average, and may likely flatten after. ICER recommends using a constant HAQ degradation beyond 15 years in the model. Thus, associating a HAQ change by age group without equating to duration of disease may misrepresent actual HAQ change over time. We recommend including a HAQ trajectory over the lifetime of the model in graphical or tabular format for cDMARDs and default tDMARD sequence.

4. ICER recommends including the independent effects of radiographic progression, using (modified) total Sharp score (TSS) on HAQ. While its effect may be modest, it adds clinical face validity to the model.[2-5]

5. In alignment with including the TSS relationship with HAQ, ICER recommends using OR of 1.97 (in patients with radiographic data) as reported by Wolfe et al. 2003 for the effect of HAQ on mortality.[6] This will result in log odds of 0.679. Please elaborate on calculations used to derive log HRs for a 0.25 unit-increase in HAQ, since the Michaud et al. 2012 study reports this unit increase annually after the first six months. Please provide justification on assuming the same log HR for a 0.25 unit-increase in HAQ after 36 months. An alternative approach to derive RA-specific mortality is to use the equation:

   Mortality rate = Mortality from life table*1.33^{HAQ}, which has been used in another RA model.[7]

6. Elaborate on the rationale for assuming a normal distribution of HAQ rebound between 0.7 and 1 in the default settings. In the absence of evidence on HAQ rebound following treatment discontinuation, ICER recommends a conservative approach assuming 'rebound' to baseline HAQ when prior to subsequent treatment initiation.

7. Elaborate on the model validation process since section 10 is lacking details. Recommend providing details on all validation processes and results, following the ISPOR/SMDM recommendations.[8]

Minor

8. Revise notation throughout the document, including in the appendix, for consistency. For example, the use of "T" as a variable or to symbolize the transpose of a matrix, the use of commas in subscripts or not, the use of each Greek (and Latin) letter to represent a specific parameter rather than being used to represent different parameters in different equations, among others. The consistent use of notation would add clarity to the document.
9. Include an impact inventory for societal perspective, including the elements identified as important but not included due to lack of data or other limitations.
10. Revise Algorithm 1 for clarity and completeness. For example, there are several "if" statements without corresponding "else" statements.
11. In the online version, provide guidance on the appropriate distribution to use for time to treatment discontinuation. While allowing for 7 distributions enhances flexibility, it also adds confusion for users who cannot easily see how well the model fits the data.
12. The online simulation model is slow and prone to time out. If this version is to be implemented more widely in practice, we suggest improving the efficiency of the R coding, switching to a server faster than the current Rshiny server, or considering the use of meta-modeling/emulator techniques.
13. We suggest adding relevant citations in Section 1 to support current challenges with using and disseminating models.
14. We suggest including costs and probability of TB. While these estimates aren't key drivers of model results, they offer clinical face validity.
15. Use data available for most agents on specific rates of serious infections, rather than a summary rate.[9-11]

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February 16, 2018

Submitted electronically to: **research@thevalueinitiative.org**

Darius Lakdawalla, PhD
Executive Director
11100 Santa Monica Blvd, Ste 500
Los Angeles, CA 90025

Re: Feedback on the Innovation and Value Initiative's Open-Source Value Project Model for Rheumatoid Arthritis

Dear Dr. Lakdawalla:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide feedback on the Innovation and Value Initiative's Open-Source Value Project model for rheumatoid arthritis.

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality healthcare. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient access to approved therapies and appropriate clinical care.

IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of more than 800 physician advocates committed to patient access. IfPA is a 501(c)(3) public charity non-profit organization.

Approach to Value and Effectiveness Models

Too often, cost-effectiveness analyses exclude patients and their health care providers from the very calculations that determine whether they can access necessary diagnostics and drugs. Models that are shrouded in secrecy and findings that are conveyed in cumbersome, inaccessible language leave patients feeling overwhelmed and excluded.

IfPA is pleased to see that IVI has taken a different approach.

The open-source framework not only welcomes input from all stakeholders, but also allows them to customize measurements to reflect their own unique values. This far exceeds the usefulness of a static, inaccessible framework.

Comments on the Rheumatoid Arthritis Model

IfPA is pleased to see that IVI's rheumatoid arthritis model accommodates factors that matter to patients, such as whether a therapy is delivered orally or via IV, and the impact of different therapies on productivity. These are major factors in patients' experiences with a given therapy.

The model's level of customization is valuable for physicians and patients, who will be able to assess with a new level of precision how different therapeutic options will impact patients, and what costs and secondary factors make for the right choice. The model also acknowledges an important reality for rheumatoid patients and providers. A single therapy seldom proves effective for a patient's lifetime. Comparing a series of alternating therapies makes for a more realistic, reliable model.

As IVI works toward perfecting its model, developers may want to simplify the interface to account for users' varying levels of understanding about economic modeling. For instance, developers might consider visualizing results with icons and images that relate to the factor being quantified rather than using bar graphs.

It might also prove helpful to divide some steps into smaller sub-steps, allowing more context for each. For example, the page dedicated to "Clinical and Economic Outcomes for Patients" might be more accessible to patients if it were broken into functional status, life expectancy, and other components as individual pages. A summary page at the end of this section could synopsize the findings together.

Conclusions

IfPA commends IVI for working toward an open, customizable value framework that can be both useful and usable to a range of stakeholders, including the patients who feel the impact of cost-effectiveness analyses on their health plan coverage.

If IfPA can provide further feedback or information regarding these comments, please contact us at 202-499-4114.

Sincerely,

Brian Kennedy
Executive Director

Janssen Scientific Affairs, LLC
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Date: January 17, 2018
RE: Innovation and Value Initiative (IVI) Rheumatoid Arthritis (RA) Model - Response to Request for Public Comments

The following information is provided in response to request for public comment and is not intended as an endorsement of any usage not contained in the Prescribing Information. For complete information, please refer to the full Prescribing Information for each product, including the following sections: BOXED WARNING(S), INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS.

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General Comments

The model contains a critical error because it does not consider SIMPONI ARIA as a treatment option. While the model does consider SIMPONI subcutaneous (SC), it is important that the developers of the IVI model recognize that SIMPONI SC and SIMPONI ARIA are entirely different formulations each with different pharmacokinetic, efficacy, and safety profiles, separate Phase 3 trial programs, and with separate US labeling as determined by the FDA. These products and their respective data sets must be considered separately (See attached SIMPONI Prescribing Information, SIMPONI ARIA Prescribing Information).

According to the report, comprehensive options to test different structures, data and assumptions are included in the model. However, in the online interface, the users do not have access to the options described in the report, and it is not clear what structure, assumptions and data sources are used in the online interface model. The danger in this is that the online interface may invite exploration without context or full understanding of how variables in the model relate which may cloud interpretation of results. For example, model assumption H2 (Stephens et al, 2015) uses methodology that is highly specific to patients with early aggressive RA, a population that was not tested in trials of golimumab or infliximab and most other biologics. This may be why significant variation in change in HAQ progression is noted with the H2 model assumptions vs H1 and H3.

In general the model in its current state may be too complicated for non-expert users. Language should be added to the online version to caution use by those unfamiliar with modelling methodologies.

Overview of IVI RA Model

The IVI-RA model is not a value assessment framework but a model that simulates the costs, health outcomes, and risks associated with treatments for RA. It can therefore be used with any value framework preferred by the user. The online tools support both cost-effectiveness analysis (CEA) and multi-criteria decision-analysis (MCDA).

Value Assessment

In MCDA, number of serious infections is included as one criteria. However, serious infections are also included in the CE model and have cost and quality of life impact already. The impact of serious infection in the value assessment appears to be counted twice. It should be removed from either CE model or the MCDA criteria to avoid double counting.

Populations

Page 18, Paragraph 2- Data from the CORRONA registry may underestimate the disease burden in the US RA population related to disease activity and physical function. Note Table 2b in Curtis et al which shows lower HAQ and CDAI scores compared other data sources. We recommend not depending on a single source in order to avoid outliers and to identify mid-range estimates for population disease activity (Curtis et al, 2010).

Source Data and Parameter Estimation

1. NMA: The inclusion and exclusion criteria are not described. Trials included in the NMA differ from other published studies such as bythe Institute for Clinical and Economic Review (ICER) and the results are also considerably different. As stated previously, SIMPONI ARIA and SIMPONI SC must be considered as distinctly separate products. Missing GO-FURTHER trial data for SIMPONI ARIA are provided in Table 1 below and should be included in the NMA. Differences in patient characteristics and trial design differences are not considered in the NMA. For example, in the RAPID 1&2 trials, patients who did not achieve ACR 20 at weeks 12 and 14 were designated treatment failures and were withdrawn from the study at week 16. Other trials including GO-FURTHER called for treatment failures to continue in the trial. This leads to considerably low placebo rates at week 24 in RAPID 1&2 trials compared to other trials. As NMA did not adjust for this difference, the results are inevitably biased in favor of Cimzia (see reports published by the Canadian Agency for Drugs and Technologies in Health cited in References below). In further proof of the inflation of clinical benefit of RAPID 1&2, the head to head comparison of Cimzia vs Humira (EXXELERATE trial) did not meet its primary endpoint for superiority, and demonstrated no statistically significant difference in efficacy between Cimzia and Humira in combination with MTX in both short-term (12-week) and long-term (2-year) evaluations (Smolen et al, 2016).
2. The model considers dose adjustment for REMICADE but not for Humira or Actemra although labels for each of these products allow for dose adjustment. Dose adjustment can make a material change in the cost attributed to each therapy. Input options for dosing should be allowed from two perspectives: the average drug quantity used per administration and the average dosing frequency (or number of doses per year) during maintenance therapy. These input options to the model will allow users to understand the impact of dose escalation using their own existing utilization data.

   The following biologics have dose escalation options included within their product labels (See respective product Prescribing Information):

   Humira: Available references have found dose escalation of Humira to occur in 12.6-24.3% of patients (Fisher et al, 2013).

   REMICADE: REMICADE provides dosing flexibility for patients with RA. The REMICADE PI recommends that patients be initiated on 3 mg per kg with maintenance dosing every 8 weeks and allows dose adjustment to as high as 10 mg per kg or maintenance dosing frequency as often as every 4 weeks. In real world practice the average dose of REMICADE has been reported to be 5.5 mg per kg. See Bolge et al for dose escalation assumptions that may be more consistent with clinical practice over the course of a 12-month period (REMICADE Prescribing Information; Bolge et al, 2012).

Actemra IV Administration: When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response (Actemra Prescribing Information).

P 30, 8.4 - Rate of HAQ Progression for CDMARDs vs TDMARDs:

8.4.1: HAQ progression parameters of cDMARD-treated patients are derived from Wolfe and Michaud 2010 and are "assumed to reflect the course of progression of HAQ in the absence of tDMARDs". Our reviewers suggest that HAQ trajectory of cDMARD patients before progression to tDMARDs does not adequately represent the presumed trajectory of cDMARD patients' HAQ in the absence of tDMARDs availability. While this may be a minor issue if this estimator is used in a model run intended to derive relative cost effectiveness of differing treatment sequences including line 2 biologics, this is a minor issue it becomes more significant when the model user is interested in ascertaining cost effectiveness of tDMARDs overall, as compared to cDMARds. In this scenario, the model, and this estimator, will result in significant under-valuing of tDMARDs as this estimator will not capture true HAQ trajectory of patients in an environment of only cDMARD use.

8.4.2: HAQ progression parameters of cDMARD patients are alternately used from Norton et al 2013, 2014. The HAQ trajectory of 1 of 4 cohorts cited in this paper represent the HAQ trajectories of patients with lower disease severity, and which are partially on biologics. As with issues in 8.4.1: Use of this parameter is an imperfect match for the decision analytic question that this model seeks to address. Similar to above comments: If the model user intends to compare relative cost effectiveness of two biologics after a presumed 1st course of cDMARDs (as a treatment sequence comparison), then this estimator mismatch may not present as significantly biased to cost effectiveness between tDMARDs. If, however, the user is interested in the question of overall cost effectiveness of tDMARDs compared to cDMARDs, then this parameter significantly underestimates the presumed HAQ trajectory of a general population on cDMARDs who have not accessed tDMARDs. This will significantly under-value the utility of tDMARDs.

The validity of this model to evaluate overall tDMARD cost effectiveness versus cDMARD is seriously compromised by the lack of a HAQ trajectory parameter than truly measures expected HAQ trajectory of cDMARD patients in the absence of tDMARD availability. This key parameter may be derived from data that may be available for HAQ trajectories before tDMARD introduction (eg from 80s or 90s), or from recent patient data from countries where patients may not have had access to tDMARD treatment, but for whom the imperative of aggressive early treatment via cDMARDs may have been presumably understood.

P 41 – HRU Costs are derived from citations in the literature and are inflated to 2016 values. This may lead to inaccuracies since literature citations used may be several years old. It would be preferred if inputs for more recent data could be obtained from contemporaneous databases or input by the user to minimize error introduced by inflation assumptions.

P 33 – Treatment discontinuation derived from CORRONA is an average of all anti-TNF agents, yet it is well documented that treatment discontinuation rates are higher for subcutaneously administered anti-TNF agents as compared to REMICADE. In Greenberg et al 2012, treatment persistency for bionaive patients who initiated REMICADE was 76% at 12 months and 63% at 24 months, compared to 68% and 53% for Humira at 12 and 24 months, respectively and 72% and 53% for Enbrel at 12 and 24 months, respectively. Additional sources for treatment persistency include Fisher et al 2013 and Chastek et al 2016 (references provided below). Furthermore, we have shown that discontinuation rates for SIMPONI ARIA are similar to that of REMICADE (Data on File). Persistency for SIMPONI SC was cited as 75.3% in a study by Mourão et al, 2016.

P 42, Table 16 - Wholesale Acquisition Costs (WAC) are not current for some biologics. Drugs, effective dates and WAC are noted below.

a. Enbrel- 1/1/18 $1,218 per 50 mg syringe; Humira 1/1/18 $2,436.02 per 40 mg syringe; REMICADE 2/9/17 $1,167.82 per 100 mg vial; SIMPONI SC - 1/3/18 $4,519.76 per 50 mg injector; SIMPONI ARIA (intravenous) 9/6/17 $1,652.59 per 50 mg vial;Cimzia 1/1/18 $4,044.32 per 400 mg; Actemra IV- 1/1/18 $1,042.00 per 200 mg vial; Actemra SC - 1/1/18 $984.72 per 162 mg syringe; Orencia IV 1/1/18 $1,046.25 per 250 mg vial; Orencia SC - 1/1/18 $1,032.76 per 125 mg syringe; Rituxan 1/1/2018 $903.38 per 100 mg vial; XeljanzXR 1/1/18 $4,095.64 per 30 d supply of 11 mg tablets.

b. Drugs provided through a medical benefit or Medicare Part B are typically reimbursed using Average Sales Price (ASP). The largest segment of Janssen RA products, (REMICADE and SIMPONI ARIA), are most commonly covered under a medical benefit. The ASP calculation captures the list prices and the non-statutory discounts provided for all manufacturers. ASP is published quarterly and is available on the CMS website, but lags in time by approximately 2 quarters.

c. In Table 16 (P. 42) dose escalation is assumed for REMICADE but not for Humira although Humira PI does allow for dose escalation in patients not taking MTX (Humira Prescribing Information). We recommend that the base case dosing assumptions conform exactly to the label and that the model allow the end user to vary the dosing and dosing interval assumptions rather than force the end user to compare to pre-set dosing and administration assumptions that may not be reflective of their true utilization.

d. Dosing for SIMPONI ARIA should be included:
    i. The PI for SIMPONI ARIA specifies 2 mg per kg at weeks 0, 4 and every 8 weeks thereafter (SIMPONI ARIA Prescribing Information).

e. Dosing for administration of IV Actemra should be included:
    i. IV Actemra dosing per the PI is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based upon clinical response (Actemra Prescribing Information).

Limitations and Areas for Improvement

P 8 - The model utilizes serious infection rates and changes in HAQ score during the first 6 months from baseline based on clinical trial evidence. It is known that differences in clinical trial populations and adverse event rates differ in those biologics that were first to market vs those that entered later. This could be a confounder in the model.

P 8 - The model assumes patients change treatments if they have a serious infection. This may not be consistent with real world scenarios where treatment might be held and then restarted.

P 9 - The Wailoo regression algorithm may have limitations for HAQ mapping. Pennington et al reported that the use of this utility mapping algorithm may have impact on overall results, particularly on inflation of the magnitude of the ICER (Pennington et al, 2013).

Appendices

P 67, Table A9- Add missing ATTRACT 102 week publication:

- Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with

rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum*. 2004;50:1051-1065.

P 70, Table A10- The correct n for the REMICADE 3 mg/kg every 8 weeks +MTX treatment arm is 86.

P 70, Table A10 - Add missing ACR20 and HAQ-DI data from ATTRACT at week 20 (Data on File, provided in Table 1)

P 71, Table A10 - The correct n for the SIMPONI 50 mg +MTX treatment arm in GO FORWARD is 89.

P 71, Table A10 - Add missing DAS28 data at week 24 from GO FORWARD (Data on File, provided in Table 1)

P 71, Table A10 - Add missing ACR20, ACR70, DAS28, and HAQ-DI data at week 24 from the GO FURTHER trial (Data on File, provided in Table 1)

Table 1: Missing or Corrected Efficacy Data Related to Janssen Products

Trial ID	Treatment	N	Time in Weeks	ACR20 n(%)	ACR 50 n(%)	ACR 70 n(%)	ΔDAS28 (SE)	ΔHAQ-DI (SE)
ATTRACT	REMICADE 3 mg/kg Q8W+MTX	86	30	43(50%)	22 (27%)	7 (8%)	Not available	Not available
	MTX	88	30	18(20%)	4 (5%)	0 (0%)	Not available	Not available
GO FORWARD	SIMPONI 50 mg+MTX	89	24	79 (60%)	49(37%)	27(20%)	**DAS28 CRP-** Median change from baseline (IQR): -1.682 (-2.539, -0.676) Mean change from baseline (SD): -1.621(1.2873)	-0.38 (0.16)
	MTX	89	24	25(28%)	12(14%)	5(5%)	**DAS28 CRP-** Median change from baseline (IQR): -0.624 (-1.469, 0.215) Mean change from baseline (SD): -0.692(1.3206)	-0.13 (0.13)
GO FURTHER	SIMPONI ARIA 2 mg/kg +MTX	395	24	248(63%)	138(35%)	69(18%)	**DAS 28 CRP-** Median change from baseline (IQR): -2.0441 (-2.9928,	**HAQ-DI** Median change from baseline (IQR): 0.50 (0.1250, 0.8750)

						-1.1094) Mean change from baseline (SD): -2.0402 (1.38380)	 Mean change from baseline (SD): 0.5292 (0.63743)
MTX	197	24	62(32%)	26(13%)	8(4%)	**DAS 28 CRP-** Median change from baseline (IQR): -0.5200 (-1.6840, 0.2262) Mean change from baseline (SD): -0.7419 (1.42703)	**HAQ-DI** Median change from baseline (IQR): 0.1250 (-0.1250, 0.5000) Mean change from baseline (SD): 0.2054 (0.54769)
Source: Data on File. Janssen Biotech, Inc.							

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Canandian Agency for Drugs and Technologies in Health. *Common Drug Review: Certolizumab Pegol (Cimzia-UCB Canada Inc)*. May 2010. Available at: https://www.cadth.ca/media/cdr/complete/cdr_complete_Cimzia_May-28-2010.pdf

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SIMPONI ARIA® (golimumab) Prescribing Information.

SIMPONI® (golimumab) Prescribing Information.

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National Organization for Rare Diseases

Received via email from Paul Melmeyer

Hi Mark,

Apologies for the delay. We have been able to explore the tool a bit, but I don't think we'll be able to submit anything particularly expansive before Friday. This is because it is rather RA-specific (which is difficult for us), and we frankly just don't have the time to invest in a deep dive since FDA chose to put 3 comment deadlines for the end of this week!

A couple of things I caught that could be helpful:

1. A glossary of terms would be very helpful. For example, I have no idea what "bDMARD" is, but it's referenced everywhere. Same goes for the sequence of treatments.

2. Great job including rebates and administration costs. Very nuanced, and often overlooked!

3. The "change in functional status" and "life expectancy" charts are bit confusing since improvements in the first graph are represented by negative values, but improvements in the second graph are represented by positive values.

4. On your cost-effectiveness plane, you specify the costs are per year, but you do not specify the time horizon for incremental QALYs. Perhaps I'm getting out of my CEA depth, but I was a bit confused due to the different time horizons used on that chart.

5. Will this tool work for diseases in which there is no alternative treatment? This is the vast majority of rare diseases.

6. It would be helpful to visualize the cost of each treatment parallel to the "Monetized value of each treatment sequence".

7. Some instruction on how to weigh the other "explore inputs" would be helpful. For example, perhaps population analysis on the mean weight of productivity and the other subjective values would be a good starting point. For example, the "average American" would weight productivity at 12%, or something like that. If we're starting at zero, I would have no idea what is actually appropriate. Same goes for many of the other optional inputs.

Sorry again for not being able to weigh in further, but please let us know about next steps, especially if orphan therapies are considered for this model.

Hope this was helpful!

Best,

- Paul

Pfizer

Received via email from Sachin Kamal-Bahl

As a strategic advisory board partner we are grateful for the opportunity to provide additional comments on the on the IVI RA model. We continue to see a unique opportunity in your approach to create an open source model for all to have access to. In reviewing the documents provided we present the following comments. We continue to suggest that IVI take the time to address these comments, review the changes made with the advisory board including all stakeholders, and integrate a formal process with approvals from stakeholders as you continue to advance the model forward.

For clarity we have separated the comments into sections 1) general comments 2) model specific comments.

General comments

1) We ask that IVI continue to review the principles around value frameworks that have been developed by PhRMA and NPC. These principles should form the underlying basis of both how IVI approaches model development, and what key parameters IVI seeks to advance in its models. Currently, we see significant opportunity for IVI to improve on its alignment against these principles. For example: a key consideration in both PhRMA and NPC's principles revolves around transparency in process. ICER et al largely build models behind closed doors, without gathering feedback from stakeholders as the inputs are selected. When they do release their draft findings, stakeholders are left struggling to understand complex models in often short review periods. Unfortunately, IVI has made the same errors in its process. Although additional data has been provided in this updated version, the sourcing and justification of decisions remain unclear in many instances which reduces the ability to understand or comment on the appropriateness of the specific parameters. We reiterate a strong believe in open source not only in the development of the model structure but also in the parameters used to populate the model.

2) Although, many front end descriptions have been developed the many front end tools can create confusion in the users' ability to adapt or amend data. Of significant note, depending on the front end used, there can be a lack of information on the efficacy data, data used in the model parameters, and an overall lack of clarity as the application of the correct technical documents all of which make using the model online dashboard a confusing process. Depending on the front end used there are significant differences in the changes that can be made and as such further clarity should be provided to the end user.

3) We applaud the integration of multi-criteria decision analysis and the ability of the end user to adjust prefernces weights. This is a strong addition to the tool as is specific domains as preference for treatment administration, insurance, and time since approval. We would suggest that an additional function should be the depth of indications each product has. Given that a medication which could be used in mulitpile comorbid conditions, the insurance value of the product could be improved.

4) We are happy to see greater integration of patient level information. However, while the model is recommended to be built on consensus, information on the consensus process, beyond a description of the use of patient level input, has not been provided. As noted above, we continue to suggest that IVI take the time to address these comments, review the changes made with the advisory board including all stakeholders, and integrate a formal process with approvals from stakeholders as you continue to advance the model forward.

5) As previously suggested, we would also suggest that a number of external rheumatology focused health economists should be integrated as an additional advisory board to IVI to continue to advance this model. We would be happy to submit the names of number of individuals who could provide independent, objective feedback and support to strengthen the project. This would further separate this work from past efforts.

6) IVI's objective was to develop models that were market driven; however the model as it is developed does not appear to reflect the US environment and does not seem to integrate such aspects as payer restrictions, step edits, etc. An innovative model should allow for an assessment of these processes and the impact of removing these restrictions on the identified endpoints of interest to patients, rheumatologists, and relevant stakeholders

7) Further, given access to the above data, one should use it and only resort to modeled results when measured outcomes are not present. This would make the result far more valuable to all interested stakeholders and stand out from past efforts to this end.

Model specific comments

1) Model Data used

   Given the maturity of the data on many advanced RA therapies including advanced therapies such as Anti-TNFs, novel Mechanism of Action Biologics, and JAK inhibitors, we would suggest that a truly innovative approach should include a partnership with the developer of an established observational data set to better achieve the outlined goals of a transparent, market driven, multi-perspective model. Similarly, we recommend that data be requested from stakeholders (industry, payers, and registry owners) which also could inform the model(s) being developed. Regardless, it would be preferable to integrate a real world data set/registry which could report on the changes of disease activity and likelihood of switch to better reflect the treatment patterns in the US.

2) Model structure
   a. The switching methodology and justification for treatment switching is poorly outlined and does not reflect current clinical practice or how physicians make the decision to change therapy in the US healthcare system. Most notably it ignores the treat to target ideology as recommended by the American College of Rheumatology.
   b. The report refers to the 336 possible model structures, however many of these structural changes are based on the estimation of how HAQ is derived (either by ACR response, or EULAR response) or treatment response is determined (ACR,

DAS28, SDAI, or CDAI). This appears to be an attempt to integrate the methods of efficacy of a number of other published CEA models rather than building a consensus on one type of structure/modelling method. Also, as outlined further the transformation from ACR to other variables of effectiveness is flawed.

c. The issue of taking a categorical variable ACR 20/50/70 response to a continuous variable such as SDAI, CDAI, DAS28, and HAQ is not clearly outlined or described in the document. Algorithms for mapping the ACR response to SDAI, CDAI, DAS28, EULAR response, and HAQ are taken from a number of different, small mapping trials which may or may not show valid relationships between the measures. This limitation was discussed in detail in the document, but further information and variability in the estimates (and the distributions which could be used in the PsA) should be included in the description and model.

3) Patient population
   a. The initial data on the patient population were taken from Curtis et al and US301 Clinical trial. Of note is that is unclear which of the US registries reported on in Curtis et al is being used and it appears that difference data points (age, HAQ score, etc.) are taken from different registries without a single registry's data being identified as the seminal piece of patient characteristics. Similarly, reviewing the data from Curtis et al it is unclear of when characteristics were collected- at the time of treatment initiation or registry recruitment. A more appropriate source of data would be a real world registry which would report on the clinical characteristics of a patient population starting an advanced therapy. These data should be easily accessible through collaboration with a US registry such as Corrona.
   b. It also questionable to take the data from a leflunomide (a csDMARD) trial completed published 14 years ago- US301 -to inform a model designed to report on advance therapy utilization. This trial and trial data may not reflect the current patient population or treatment patterns based on disease activity. Furthermore, the work completed by Smolen et al only for reported on the validity of SDAI not CDAI.
   c. The algorithm for distributions used in the heterogeneous patient population also could have been replaced simply by using a patient population taken from US based registries who are initiating an advanced therapy. Similarly, the use of a RWD source of advanced therapy experienced (referred to as a bDMARD experienced) patients could inform on the baseline characteristics for those patients when entering the model.
   d. It is also noted that disease duration is included in baseline characteristics of RCTs and is integrated in CEA models. The justification of omission of this variable in the patient populations should be better articulated. Given that disease duration is identified in the latent class growth model for HAQ progression as a key variable it is unclear how that has been integrated into the model.

4) Comparators

a. We question the use of csDMARDs as a comparator for anything other than salvage or last line of therapy. A patient whose disease would necessitate an advanced therapy is likely to receive that therapy and while economic theory does propose a "do nothing" strategy we feel this is both an unethical and unlikely strategy and does not reflect clinical practice. Engagement with the recommended panel of RA specialists would help clarify this point.
b. As described in the general comments, the structure of the model does not appropriately describe the system in the United States for an RA patient. The current formulary and PBM processes which often include preferential products which impact available treatments. A more appropriate model would include data reflecting that and changing the process to assess the impact of these step edits and restrictions of products.
c. It is also noteworthy that although many treatments for RA have the opportunity to increase dose or decrease the time between doses, this is not included in the modeling. Again, a number of studies using evidence from registries/observational data has reported on this topic and could be integrated into the model.

5) Efficacy data
   a. Initial treatment response, within the model for the initial 6 months of any treatment the estimated response was taken from a newly completed IVI Network Meta Analysis (NMA) using only using RCT data. However, very little information on the NMA is available, of specific note is the background information on the methods of study selection, the studies and data included in the NMA, and methods employed to run the NMA. It should be recognized that a number of registry, non-RCT, and observational trial data sources exist which include US and non-US populations, however, based on the limited information provided it appears that these data have been excluded from these NMA and therefore are ignored. This appears to go against the ideology of reflecting the current US market/being market driven.
   b. For the initial treatment phase it is further unclear why only RCT data were used when other components of the model integrate observational data (i.e. Adverse Event data, initial populations, relationship between HAQ and costs of RA). Given the long history or data and the integration of other registry data in other aspects of the model (i.e. Adverse events), it is unclear why a NMA was required and one so restrictive of inclusion criteria.
   c. Similarly, it is unclear why a factor was applied for the reduction of initial treatment response when patients in the model are assumed to have previous biologic or advanced therapy exposure (either because they have switched treatments in the model or entered the model with the baseline characteristic of having previous advanced therapy or biologic exposure). A number of RCT studies and observational data sources exist to more accurately estimate the different efficacy for a patient who has been exposed to previous biologic or advanced therapy vs a patient who is naïve to these treatments. These data are

ignored by this model (or else perhaps have been inappropriately integrated into the NMA).

d. In the description of efficacy and progression of disease in the period after the first 6 months the method described a number of sources of data. Many of these described methods have been used in previous cost effectiveness models, but appear to ignore the progression of the disease and the natural path of RA observed in clinical practice.
e. For the data on the HAQ progression (in absence of or in the presence of bDMARD or tsDMARD) these data are taken from a number of different registries and sources of data nationally and internationally. Again, a partnership with a US registry or source of real world data would better articulate the disease progression, as well as provide greater information on the thresholds of change for switching treatments.

6) Adverse event reporting
    a. Using a single adverse event (serious infections) does not represent the many events, many of which may require healthcare resource utilizations, and may or may not require discontinuation of treatment. A number of trials (observational and RCTs) and registries have reported on the safety of the treatments included in the model. Using a single adverse event, having it cause a change in treatment, while this is stated as a model limitation, this does not reflect clinical practice. Furthermore this ignores a number of studies which have been completed in RA patients receiving advanced therapies reporting on the risk and changes in risk reported by treatment for a number of unique adverse events and co-morbidities.
    b. Additionally, it is assumed that the risk of adverse event is identical for all treatments. This also ignores a significant amount of literature on the safety of advanced therapies.

7) Utility measurement
    a. The model reports on two models for transforming HAQ score to utility. It is noted that some other methods were ignored due to the data used coming from clinical trial data. This exclusion of methods seems peculiar since clinical trial data is identified as being the primary tool for efficacy measurement. Similarly, studies measuring the impact of using different utility measures (SF-6D, HUI2/3, etc.) have been completed but were ignored in this model. Similarly a number of RCTs and registries have collected and reported on utility data which could have been integrated into this modeling exercise.

8) HAQ to mortality and healthcare resource utilization
    a. Mortality, RA-related hospitalizations, and productivity costs are all estimated from the patient HAQ score. While this has been used in a number of previous CEA models, again, there is potential to use data from an established registry or data set to continue to improve the reporting of this topic.

9) Prices and costs

a. Currently the model uses the WAC price which we feel is not appropriate. The WAC, as published by FDB represents the manufacturer's (for purposes of this Drug Price Policy, the term "manufacturer" includes manufacturers, repackagers, private labelers and other suppliers) published catalog or list price for a drug product to wholesalers as reported to First Databank by the manufacturer. WAC does not represent actual transaction prices and does not include prompt pay or other discounts, rebates or reductions in price. First Databank does not perform any independent investigation or analysis of actual transaction prices for purposes of reporting WAC. First Databank relies on manufacturers to report or otherwise make available the values for the WAC data field.
An alternative source of data would be the NADAC; it is our position that the NADAC is a more appropriate measure of drug price. The purpose of the NADAC is to create a new national price benchmark that is more reflective of the prices that pharmacies pay to acquire prescription and over-the-counter drugs. The statute provides that such prices represent a nationwide average of consumer purchase prices, net of discounts and rebates. The survey data will provide information which CMS expects to use to assure compliance with Federal requirements. A monthly nationwide survey of licensed retail community pharmacies, which will include independent pharmacies and chain pharmacies in the United States, will be performed to collect drug acquisition cost information. To ensure that NADACs are accurate, timely, and robust, the NADACs will be reviewed and updated on a weekly basis.

b. The integrated use of only productivity as the societal measure of cost may not fully articulate the costs of absenteeism, presenteeism, and other non-monetary or intangible costs. Further articulation of the costs used would assist a proper assessment of the model.

Darius Lakdawalla, PhD
Executive Director
Innovation and Value Initiative
11100 Santa Monica Blvd, Ste 500
Los Angeles, CA 90025

January 17, 2018

RE: Innovation and Value Initiative (IVI) Open-Source Value Project: IVI-Rheumatoid Arthritis (RA) Model Request for Public Comment

Dear Dr. Lakdawalla,

Sanofi-Genzyme and Regeneron appreciates IVI's efforts to solicit and integrate stakeholder feedback into the IVI-RA Model, the first project released through the IVI Open-Source Value Project. We are pleased to see flexibility of the model, in which many inputs and assumptions can be adapted by the user, and that the model is detailed in the technical document entitled, *"A Description of the IVI-RA Model v1.0."* We also commend the development team for creating multiple ways to use the IVI-RA model based on level of expertise, type of user or stakeholder, and intended use of the information. The IVI-RA Value Tool, IVI-RA Model Interface, and the iviRA R Package enhances the transparency of the Open-Source Value Project.

We recognize the extensive effort and investment of resources it took to undertake this project in a disease state such as rheumatoid arthritis. With 384 available model structures, many scenarios of interest to the end user will be accounted for by this model. Based on our review of the IVI-RA Model, our comments and suggestions below focus on the following: ***model functionality, user navigation, IVI-RA Value Tool population, treatment sequences, model structure, parameter values, cost-effectiveness analysis and future adaptations***.

Model functionality
The model interface allows the user to modify input settings in the Model Setup section. It would be helpful to have functionality built-in to allow the user the option to save the modified inputs entered into the model and to have access to the saved data upon accessing the model again or after running an alternative scenario. Similarly it would be helpful to be able to save outputs of the model results.

User navigation
The "Introduction" tab indicates that that the user can modify the simulation settings in the "Setup Model" tab, however "Simulation Settings" is found in the "Run Simulation" tab. We recommend clarifying this under Custom analysis in the "Introduction" tab. Clarity is needed to inform the user where "modify output settings" can be found. The "Introduction" tab under "View Model Results" in "Custom analysis" section implies that the user would click on "Modify output settings" to select between societal or health care sector), however it appears that the selection is made in "Value to the Healthy" and "Cost-effectiveness Analysis" under the "View Model Results" tab.

We recommend providing a statement in the Model Interface "Introduction" tab regarding where the user can find references for the default settings (input parameters), as well as alerting the user that parameters will be referenced on the "View Inputs Used in Simulation" tab. Ideally, each default parameter should be referenced on each page of the "Setup Model" section.

IVI-RA Value Tool population

Within the Value Tool, concepts are clearly defined so that the user understands the inputs, outcomes, value calculations and scenario analyses. In the "Setup" tab of the Value Tool, it would be helpful to also describe the default population simulated in the tool for those decision-makers who do not intend to make adjustments to the parameters on that tab. This will assist the user with a better understand of what is being reviewed when "Pick for me" is selected and assist with appropriate utilization of the data.

Treatment sequences

KEVZARA® (sarilumab) was approved by the FDA in May 2017 for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs).We therefore recommend consideration of its inclusion in the treatment sequence of the model. For more information, please refer to the KEVZARA full prescribing information, including **Boxed WARNING**. We would also like to recommend the user have the capability to add new medications, dosage forms and frequency to the model in the event approval is granted prior to model revision.

Model structure

While the IVI-RA Model is very flexible in the model structure, we would like to recommend that users have multiple options for utility equations, in addition to the Hernandez-Alava mixture model and Wailoo logistic regression equation. Other options for consideration can be found in cost-effectiveness analyses such as Bansback et al. 2005, Hurst et al. 2006, Malottki et al. 2011, Brennan et al. 2004, Ducournau et al. 2009, and Boggs et al. 2002 (Table 1). Similarly, we recommend the flexibility of modifying mortality rates based on the impact of baseline functional status on mortality, as suggested by Yelin et al. 2002, Michaud et al. 2012, Diamantopoulos et al. 2012, or Marra et al. 2007.

Table 1. Examples of Utility Equations*

	BRAM	Abbott	Wyeth Pharma-ceuticals	Schering-Plough Ltd	Roche	Bristol-Myers Squibb Ltd
Mapping of effectiveness data to utility	Quadratic equation using dataset supplied by Hurst and reported in Hurst et al. 1997 in the absence of any more recent dataset available to the assessment group	HAQ scores were converted to EQ-5D scores according to equations (linear and non-linear) developed by Ducournau et al. 2009 using data from TOC trials. The non-linear equation was used for the base-case analysis, while the linear equation was examined in sensitivity analyses	HAQ scores were converted to EQ-5D scores according to a linear equation developed by Brennan et al. 2004	Utility was estimated to be a function of EULAR response, treatment (on biologic treatment or not), health-state utility at time of treatment initiation, age, disease duration, number of previous DMARDs and gender	HAQ scores were converted to EQ-5D scores according to the non-linear equation developed by Ducournau et al. 2009 using data from TOC trials	HUI 3 utilities were calculated from the HAQ based on a conference abstract [Boggs 2002] EQ-5D utilities calculated from HAQ were used in a sensitivity analysis

**Source: Table 74 Data input and assumptions used in manufacturer models Malottki et al. Health Technol Assess 2011;15(14)*

Parameter values

The user is allowed to adjust multiple parameters within the Treatment Cost section of the model interface, including accounting for a discount (lower and upper). An additional functionality of accounting for patient copay may be appreciated by some stakeholders/decision-makers using the model interface as well as in the Value Tool.

While users are allowed to adjust parameters for time to treatment discontinuation, we recommend allowing for customizable treatment discontinuation event rates for each medication included in the model. This provides greater flexibility for the user to incorporate real world data reflective of their organization.

Cost-effectiveness analysis

The model results section provides an extensive number of results allowing potential users a variety of data to select and utilize based on their organization's specific needs to inform decisions. Within the cost-effectiveness analysis section, some users may be interested in viewing individual medication incremental cost-effectiveness ratios (ICERs) rather than seeing the ICER of sequences in order to inform decisions. We recommend the incorporation of individual ICERs in addition to sequence ICERs.

Model Interface

In the Model Interface, we are unclear about the adjustment of the initial treatment effect according to treatment line. Specifically, how are the low and high values of the adjustment factor applied in the model? Additionally, while the Model Interface is geared toward experienced modelers, there are some parameters such as the ACR and EULAR response rates for initial treatment responses that are not

available to the user. Instead, the user is given the parameter estimates of statistical models (such as the Bayesian models for ACR and EULAR response rates), and therefore must perform calculations to understand the response rates used in the model. We are unclear how the user can enter alternative response rates.

Future adaptations

We appreciate the thoughtful construction of the model which facilitates utilization by a broad set of stakeholders within the US healthcare system. While the US healthcare system is the focus of the IVI Open-Source Value Project, a model further adjusted to allow for ex-US adaptations in the future would be of interest.

In conclusion, we appreciate IVI's effort to incorporate stakeholder feedback as an important part of the Open-Source Value Project's iterative process using an ongoing cycle of public feedback, expert review, revision, and re-release, and its willingness to engage in such a manner for all models constructed through the Open-Source Value Project.

We look forward to further discussions and encourage IVI to continue its efforts to apply scientific principles to the study of value in medicine and create open-source tools that support decision-making and inform health policy.

Yours Sincerely,

Sheila M. Thomas
Senior Director
Global Health Economics & Value Assessment
Sanofi

Vera Mastey,
Executive Director
Health Economics and Outcomes Research
Regeneron

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Tufts University

Received via email from Peter Neumann and Josh Cohen

Hi Darius,

The IVI RA model is impressive. The range of "knobs" made available to the user to see how results change in response to alternative assumptions and outcome measures is fantastic. The interface is easy to follow, and the generated figures are great. Likewise, the technical documentation is very good.

I do have several relatively minor comments:

- While the simulation is running, it would be good to have a dynamic display indicating that something is happening. Conveying the progress towards completing the requested total number of iterations would be even better. When I first started playing with the model, I wasn't sure it was really working and started clicking on things before the simulation completed.
- The model allows the user to assign a negative dollar value to a QALY. I think the lower bound on value should be zero.
- One aspect of the navigation that wasn't clear to me was how to easily get back to the home page, or the page where the user can start the simulation. It should be easy for the user to "bail out" at any point and start all over again.
- It would be nice to be able to easily download generated figures and the underlying simulated values. That functionality may be there, but I may have missed it.
- While the technical documentation was very good in general, it could be a little clearer about what's going on with the PSA. Is each individual simulated multiple times with random draws for uncertain parameters? Does the simulation do anything to separately characterize heterogeneity (differences between individuals) and uncertainty (results that vary because of imprecise knowledge)? For example, it would be nice to know the median number of QALYs gained, and how uncertain the estimate of the median is.
- Finally – it's great, and absolutely crucial that the user has access to the source code. That means that a party that is concerned with RA (and well-resourced) can ultimately see exactly what the IVI model does. This model is very complex, however, and it would be good to provide at least some indication of how a more intermediate technical user can find his or her way around the model. For example, I am familiar with C-sharp and a number of other programming languages, but I couldn't find my way to the "top" of the model stored in GitHub. Admittedly, programming isn't my main expertise, but I feel that even someone at my level should be able to get around the model more easily. I am not saying that IVI needs to provide substantially more documentation. But something to get people started would go a long way.

-Josh