I like to always start with a case and the case today is a case of rheumatoid arthritis and this is a lady that I cared for – for quite a long time and she developed initially joint pain and swelling and was noted to have an elevated rheumatoid factor CCP and an elevated CRP and SED rate. And she had rapid improvement of her symptoms with Prednisone which is usually expected but unfortunately Prednisone is oftentimes not a long term therapy for these folks and so we try to place them on other agents. We had a difficult time controlling her disease and eventually I remember one of the most poignant moments in taking care of her was when she had to decide that she wasn’t going to work anymore. And she actually later developed a very devastating complication of the disease which was interstitial lung disease.

And so let me ask you this question, this is kind of a gimme. Among common chronic illnesses which disease is associated with the lowest quality of life. I think, we’ve got a distribution, I was hoping you’d all say rheumatoid arthritis. Actually the first two answers actually were the ones that I would have actually probably picked. I was very surprised by this. And so it actually turns out though that it actually is rheumatoid arthritis and let’s talk about why.

So rheumatoid arthritis affects an estimated 1.3 million Americans. Within 10 years of diagnosis 35% of rheumatoid patients will be work disabled, it’s also associated with a reduced life span of 5 to 15 years and its associated with economic losses to the U.S. economy that were estimated in 2008 at 58 billion dollars and to put this number in perspective I looked up in Wikipedia the gross domestic product of most of the world’s nations and fully 2/3 of them are below 58 billion dollars.
And so as we talked about in the last slide it’s associated with the worst quality of life among the common chronic diseases that are out there that we think about everyday. So it’s a very significant problem for patients. Now I’m not going to emphasize too much on the pathophysiology of the disease but I want to point out that studies in the 1990s emphasized the role of cytokines and other immune effectors in the development and perpetuation of synovitis that’s exemplified by this complicated diagram here. Your not supposed to be able to read the details of. And then in the last decade we’ve come to identify citrullinated proteins as targets for autoantibodies in this disease and this has led to many new hypotheses about the pathophysiology of rheumatoid arthritis and it’s led to important diagnostic tests and I think will lead to important treatments in the future.

So let’s talk a little bit about the treatment of the disease. The studies on pathophysiology led to the development, an FDA approval of 9 biologic therapies targeted at cytokines and other parts of the immune response. This is in addition to some of the many oral agents that we already had to treat the disease. In the 1990s treatment paradigms shifted and included combination therapies and this is exemplified by the work of Jim O’Dell and the RAIN network of physicians that he put together and this resulted in an important publication in our field in the New England Journal.

And then really in the last decade what we’ve been emphasizing are new treatment paradigms that emphasize the early treatment of rheumatoid arthritis and treat to target strategies and I’ll talk a little bit more about what I mean by treat to target strategies as we go along. And two of the more prominent studies in this area are the BeST Study and TICORA.
So here’s another question for you. As we think about how do we use all of these agents, these new drugs that we’ve identified, how do we incorporate strategies for treatment, the so-called treat-to-target strategy into our paradigms for treating this disease in the usual care settings. One begins to think about what agencies within the government and elsewhere are going to be able to support doing this kind of research so that we can figure out what the best things are for patients to do.

This one is kind of tricky. And I did it this way on purpose. So which government sponsored entity does not fund comparative effectiveness and/or drug research? Okay, I hope you’ve all guessed and so actually yeah, the correct answer is the Institute of Medicine. You might be wondering well what does the FDA do here because a lot of you picked that and that’s the tricky part. And so that’s the and/or drug research. They actually have an orphan drugs program where they sponsor drug research. It’s not exactly comparative effectiveness but the point here is that the Institute of Medicine is there to provide us with guidelines and advice about how to move forward and then actually the ones that people are looking to for guidance as we think about what to do. HRQ is very intimately involved with comparative effectiveness as is the NIH and this new entity that we’ve all been introduced to recently the PCORI which is focused on patient-centered outcomes in research.

So let’s talk about what comparative effectiveness is and how do we think about incorporating it into the usual care of rheumatoid arthritis patients. And so the Institute of Medicine in 2009 after the, after a mandate from Congress developed these set of guidelines and what they said was that the
comparative effectiveness research is a generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care. The purpose of comparative effectiveness research is to assist consumers, clinicians, purchasers and policy makers to make informed decisions that will improve healthcare at both the individual and population levels and then very nicely in the description of this it was published in the Annals of Internal Medicine by Harold Fox, he pointed out the two key elements that are embedded in this definition of the direct comparison of effective interventions and their study in patients who are typical of day to day clinical care. It’s this here that I’m talking about when I say usual care is how I’ll often refer to it in this talk.

Then also to emphasize the importance of musculoskeletal conditions, the importance of the biologic therapies that we use, the Institute of Medicine created a list of CER priorities and in that first quartile among the more prominently featured priorities they included, to compare the effectiveness of different treatment strategies of introducing biologics into the treatment algorithm for inflammatory diseases and included in that of course was rheumatoid arthritis. And they also decided on overall research priorities and the tenth most important one in their opinion was musculoskeletal disorders. This one over here is health delivery and some of what we’re going to talk about relates directly to health delivery in terms of what we’re talking about for our program.

And so in terms of how does this effect rheumatoid arthritis, one of the things that I think is important is to understand what the latest treatment guidelines are or recommendations are. And to
look at those recommendations and decide whether or not there are areas for improvement or areas where the recommendations don’t have solid proof behind them. And so these are based on an international task force, this was published in the Annals of Rheumatic Diseases and Joseph Smolen and colleagues put this together and among those, among the four priorities or four recommendations that they made were the following: that the treatment must be based on a shared decision between patient and rheumatologist. The primary goal is to maximize long term health related quality of life to control the symptoms, prevention of structural damage, normalization of function and social participation. And importantly you had to abrogate information to achieve these goals and treatment to target strategies were what they recommended to optimize outcomes in rheumatoid arthritis. So as part of that they made ten sort of sub-recommendations and what found most interesting about this and part of the reason I’m emphasizing this here is that when you looked at those ten individual items, these are sub-items off of the bigger item, it turns out that the category of evidence supporting all of these task force recommendations is actually not very strong.

In other words, ideally you would like these to be category one and the strength of the recommendations to be As but most of these actually fall into the C and D categories. Suggesting that an awful lot is not known about how best to deliver care to rheumatoid arthritis patients in particular.

So really as part of that I – when we kind of like set out to do this work I sort of put in front of myself sort of what are some of the really broad important questions that we have to answer. And
so how do patients and physicians select the best therapies when there appear to several roughly equal options so going back to this concept that there are nine biologic therapies out there, how do we pick the best ones for our patients. Then also what are the best treatment strategies to achieve both the patients and the physicians treatment goals. So right now this concept of treatment to treat the target has been talked about widely but the evidence behind it is really based on very controlled studies and it’s never really been put forward into usual care settings.

And so from that was born RACER as we called it and this is Rheumatoid Arthritis Comparative Effectiveness Research. We’ve developed a program based around this concept, this involves myself, Larry Moreland, Steve Wisnewki who’s in the School of Public Health and then Dan Solomon who’s at Harvard University. And I want to point out that funding for this initially was provided by the NIH as part of the Recovery funds and then Genentech has very graciously stepped in to support this for another several years as a way of keeping this program going. The NIH was very clear in the beginning that they weren’t going to be able to support these types of things long term and they encouraged us to go out and find alternative funding.

So let me tell you about the team of folks that are involved with this. There is a group of coordinators, laboratory technicians who handle blood samples related to the project, there are Fellows that drive much of the intellectual aspect of what’s going on here and then there’s importantly a data management programming and statistic team which is led by Steve Wisnewski
and then also which includes Melissa Soll who’s not specifically under Steve but operates the interface for us with the MARS medical record system.

I also want to point out some other very important folks to making this all work. We have a physicians working group, there are 25 individuals who in addition to the ones listed in previous slides, who contribute patients to this database. This is integral to what we do in terms of making this work and the importance of this is that several in fact the majority of the patients come from practices that are really what would be more considered typical of private practices rather than typical academic practices. And so although they’re part of our academic mission, these folks operate in a way that is more similar to what you would see elsewhere.

So what we did when we set this up is I wanted to make it very simple, we didn’t want to miss a lot of patients and so we made the inclusion criteria as simple as you had to be over 18, this was to avoid juvenile rheumatoid arthritis cases. And then we asked physicians to simply tell us whether they had definite probable or likely rheumatoid arthritis patients. And we’ll come back to this in a moment and I’ll show you just how good actually it turned out, their judgement was about these patients in terms of how well they fit criteria.

We do all of our data collection on tablets, these tablets are used to administer questionnaires to patients and for the physicians. The patients fill out a RAPID3 which is a multidimensional health assessment questionnaire, sort of questions primarily that measures function. We also do a quality of
life measurement and a work productivity survey and the physicians count tender and swollen joints and provide an estimate of global function for the patient.

We also extract information from the electronic health record, really central to this process in our opinion is trying to merge all the valuable data that’s in the medical record with what we’re collecting from patients. And so we get the information on a variety of different categories. And then we also collect blood for bile markers and this would be a subject of a whole different talk than what I’m going to talk about today but this blood goes to my laboratory, it’s processed and put away for research.

Really one of the hardest things that we had to work out was how the data is all managed and how the data moves around. I want to point out that central to this is MARS in the sense that MARS is the interface between the medical record and the repository for the research information that we collect. It ____ all the activities that occur up here in blue or activities where patient identifiers are involved and what we’ve been very careful about is trying to separate who has access to those patient identifiers from folks that do not need access to it. And in particular those in the laboratory that don’t need it, those in public health doing the statistics don’t need access to it and so we put up barriers so that that type of information doesn’t flow easily between the groups of individuals.
And the registry’s targeted enrollment was 1000 subjects. And I can, we started this in February of 2010 and to date we’ve enrolled 937 subjects and we’re on target to complete enrollment by December of 2011.

What I’m showing you here is new enrollments and then followup visits layered on top of that. So the new enrollments have slowed over time. We actually and I’ll show you – I won’t actually – well we’ve had other ways of trying to estimate how many patients are in the system and our current estimate is there’s about 2600 patients that we could potentially capture so we’re actually getting it up into the range of about one third to half of all patients that are seen here who have rheumatoid arthritis. I think that’s why enrollments easing off but we’ll make our target.

So one of the things that we really wanted to test or understand initially was whether or not this was really necessary. And so, you know, what is the real rationale for having a program like RACER. So one of those is that traditional clinical trials are very expensive to perform and then traditionally industry sponsors have been reluctant to funding conduct comparative effectiveness studies. Now that’s changing a bit in all fairness but traditionally there’s always been this reluctance to compare one’s drug to another for a variety of reasons. And then the other one is that the population treated in traditional clinical trials differs from the patients in our clinics. This was always something that’s been said but we really wanted to take a little bit better look at that and see if that was applicable to our situation.
So Aarat Patel who’s one of the Fellows that I showed you on an earlier slide developed a research agenda that included a comparison of our patient characteristics from randomized control trials to our registry data. And so what he found, and the long and the short of it is, is that our patients did indeed differ. What he found was that when you compare them to data that’s been published from randomized control trials, he found that subjects in our study were older, have longer disease duration and interestingly over all had lower levels of disease activity. This actually makes sense in retrospect because really when you do trials you’re looking for, usually the sickest folks because you want to see the most dramatic effects of your drug.

And that actually also they also, oftentimes, had a much better quality of life. And so this is, I think this is really important to understand because what this means is that their ideas about what risks for example that they would like to take with the drug, probably very different than somebody who has very high levels of disease and has a very low quality of life. And so I think that this provides a really strong rationale for why you have to do this kind of research in populations like this as opposed to only doing it in populations that are much sicker. So once again it seems likely that the dynamics governing medication selection will differ substantially for rheumatoid patients in usual care setting based on this information.

So here’s another question. And this, so what I’m doing is as I walk through this next set of slides I’m sort of building what I would call the infrastructure or how RACER will function and how we
will do our measurements of patients in terms of whether or not they have the disease, whether or not – and also measuring their disease activity for example.

So one of the next things that we wanted to look at was criteria for a diagnosis of rheumatoid arthritis and right about the time we started this a new set of criteria came out and so from this I developed this question and I’ll ask you why did the ACR which is the American College of Rheumatology and EULAR which is the similar European organization recently develop new criteria for the diagnosis of rheumatoid arthritis and these are your answers over – potential responses over here on the left, hopefully most of the rheumatologists in the audience will get this

So most of you said number one and one is indeed the correct answer. And really what they wanted to do was take advantage of the fact that there’s a new test out there, the anti-CCP and they also wanted to emphasis early disease because as we get better at treating this disease we’re seeing people at earlier and earlier stages of the disease. And so Aarat, again he developed another program to look at some of this issue of diagnosis. Once again supporting most of the basic concepts of what we’re doing here. This is one of his abstracts, the 2010 Rheumatoid Arthritis criteria versus the older 1987 criteria and the Where the Real Criteria Please Standup and so what the underpinnings of this is that once again in 2010 these new criteria were developed. The new criteria were designed to diagnose rheumatoid arthritis at earlier stages and include anti-CCP testing. And then importantly the older criteria, the 1987 criteria relied more on features associated with chronic disease.
And so really his question was is how well do the new 2010 criterial work in usual care settings and part of his rationale for doing this is that a lot of the criteria was based on clinical trials. And so when physicians presented with cases, when physicians were, when the criteria were actually tested they were tested against clinical trial data and they hadn’t been formally tested in the context of usual care settings.

So let me just point out this is kind of also part of the educational mission of what we’re doing here. This is what the old criteria were, you needed four out of these seven criteria for a diagnosis of definite RA and criteria 1 through 4 had to be present for greater than 6 weeks. And I want to point out that two of these criteria, nodules and radiographic changes tend to be things that happen in the long term and they’re not short term features generally of the disease.

And the new system is based around point system that includes domains of joint involvement, serology, symptom duration and acute phase reactants. And you need a sum total of 6 points from the points that are listed here to have what would be considered definite rheumatoid arthritis. And you’ll notice here that there’s, you get more and more points for more joints that are involved, high positive rheumatoid factors and CCP, this is another name for CCP, also give you quite a high point total and then you need a abnormal CRP and SED rate and disease duration that’s greater than six weeks. But you’ll notice that you can actually meet criteria even if you have not had symptoms for up to 6 weeks in this new system.
So what did Aarat do? He took our database and he looked at the criteria. At the time that he did there were 623 patients that he looked at in detail. He found that 86 percent of them met both criteria, 5 percent of them only met the 1987 criteria, 4 percent the 2010 and then he had some others where he indeed thought from reading the records and it was also the opinion obviously of the caring physician that they had likely rheumatoid arthritis and then he had 17 patients where he had insufficient data.

He found when he compared these groups, he found that when he compared those that met both criteria that they actually tended to have the longest disease duration of any of those groups that I just showed you. And that actually those meeting the ’87 and 2010 criteria tended to have shorter disease duration. He also found that patients who met the 1987 only criteria tended to have less active disease as assessed by the CDAI disease activity measurement. And I’ll talk about how this disease activity measure is performed in a few moments.

He also did post-hoc pair-wise comparisons between the groups and he found that when you fulfill the 1987 versus the 2010 criteria, that there were differences between the groups in terms of CCP levels, large number of joints being affected and morning stiffness. And as you might expect he found that subjects, that the use of 2010 criteria identified some subjects that would not have been classified as RA otherwise, I pointed that out a few slides ago. And that importantly based on the data I showed you on the previous slide, patients with seronegative rheumatoid arthritis who had less
than 10 joints affected, once again seronegative less than 10 were captured for research purposed by fulfilling the 1987 criteria but would have been missed with the 2010 RA criteria. And so the long and the short of this is that really what these results support is the idea that our studies at least particularly in this setting, this usual care setting, should really probably continue to include both sets of criteria for identifying patients. And so we’ve taken an either/or type of approach or an and/or type of approach I should say in terms of using these criteria for identifying our patients for research studies.

So let’s move on to the concept of disease activity so I’ve talked to you about identifying the patients, the rationale for doing this research. What I want to talk to you about is what measures should we use to assess how patients are doing? And so Dan Lupash is another Fellow working with our group, took an interest in some of these disease activity measures and what was known was that people had been emphasizing the concept to treat to target strategies for optimal care patients and this suggested and once again was an underpinning of the idea that we should be using these formal disease activity measure tools for the clinical care of rheumatoid arthritis patients.

And then so really one of the questions that came up is which one of the tools that we have and I’ll go through some of the major tools that we have available, should be used in the usual care of rheumatoid arthritis patients. And then an interesting question I think was whether or not these traditionally physician-based tools could be substituted by patient tools that could actually take the place of doctors for these measurements.
This is a typical example of how we currently collect data on tender and swollen joints in the RACER registry. So we ask the doctors to fill out a form basically that involves checking boxes on which joints specifically are tender and swollen. Then we also ask the physicians to rate how the patient is doing on a scale of 0 to 10 in terms of their global perception of how the patient is doing from the point of view of their arthritis.

And there are a variety of disease activity scores that have been developed based on these tender and swollen joint counts and also based on the physician assessment, these include the DAS28, the CDAI which is the clinical disease activity index and then the SDAI which is simplified disease activity index. For simplicity you’ll notice – I’ll start here first – you’ll notice that the CDAI and SDAI are almost identical except that the SDAI includes the CRP. One of the values of the CDAI is that you don’t have to rely on a blood test for its calculation and it’s also a relatively simple equation as compared to for example the DAS. So in terms of something that could be available to you while you’re in the clinic on the day that you need it, this is the measurement that sort of stands out automatically among these three measurements that have been looked at.

The other thing to point out is that all of these measurements also include a patient global health assessment, a visual analog scale as well so it’s at least one component of this. But by and large at least most of this is heavily weighted toward the physician’s assessment of how the patient is doing.
And as you notice the DAS is a relatively complicated equation and not easy to do unless you have a calculator or a computer available.

So what’s the RAPID 3, this is a patient reported outcome that some have suggested could take the place of some of those physician based outcomes. And so this instrument has been studied only by one group at this point in time. They studied it in usual care and clinical trial settings but one of the major things that has not been looked at carefully is whether or not it’s sensitive to change in terms of patient disease activity. And then the RAPID 3 is really a composite index and it’s made up of a health assessment questionnaire which traditionally has been used as a measure of function as opposed to disease activity. It also includes patient and physician components, I mean patient components primarily that relate to global health and then patient pain. So it’s a very different instrument than the three previous instruments that I just showed you.

And so what did Dan do? So what he did was he compared the DAS to the RAPID3, he also did a variety of other comparisons, the CDAI as well to the RAPID3. And one of the striking findings in here is this is what you would have maybe hoped for at least in terms of categorization of all of these different disease activity measures, is that they would actually correlate well with one another. And so what is marked here is that these blue and green boxes are the areas where the DAS28 when it was categorized based on high, moderate, low or remission categories, how well it did when it was compared to the RAPID3. And actually I noticed that the agreement, the level of agreement is assessed by a KAPPA evaluation was actually relatively poor and we had hoped obviously that
would be higher because this would have been a nice tool to use in the clinic to replace what the physicians were doing. And actually what he found which was really striking is that the – when you looked at it this way there were a number of patients who the DAS28 suggested were in remission. Remember the DAS28 is primarily physician-based, not completely but primarily. And that there were a number of patients when the RAPID3 was done that said that no indeed, that they had, they would fallen into this moderate or high disease activity category.

So either the physician is doing a bad job which is possible, not really taking into account what the patient is interested in or there’s something else that is driving this piece up here. And then the thing to point out is that among the 127 patients in the red zone with moderate to high RAPID3 but low DAS, that they actually had more comorbidities based on the Charlson Comorbidity Index and indeed had a lower health related quality of life than the 82 patients who had a near remission of RAPID3. Interestingly there were no major differences though in terms of age, sex or disease duration between those two groups.

They also looked at these measures as a function of change and how well they correlated in terms of tracking disease activity. So what he found is that when you compare the change in RAPID3 over time versus the change in DAS28, that the correlation between that was nowhere near as strong as it is between for example the CDAI and the DAS28 suggesting that maybe this instrument is not an ideal one for measuring change in terms of disease activity. So anyway our conclusion from this is that at least for the moment our assessment of this is that the RAPID3 is not interchangeable with the
DAS28 or CDAI. I do think though that it provides valuable information, it clearly is providing an assessment of function based on the ___ component that is a big part of the RAPID3.

And the RAPID3 importantly may overestimate disease activity in patients that are in remission and low disease with more – and these patients may have more comorbidities and a lower health related quality of life. And I think that the discrepancy here is probably very important and part of the importance is that if we were just using the RAPID3 as a tool for adjusting therapy, what we might be inclined to do is overtreat people. Because really if you were driving off of people with a lot of other comorbidities and other difficulties, you may not be targeting your therapy to the actual inflammation due to the disease.

So let’s do another question – so what we’ve talked about so far once again, disease activity, criteria for assessment, now what I’d like to talk to you about is the concept of remission. In other words, what should the target be when we talk to patients, what should we hope to attain EULAR for them by giving them the medications that we’re using. Also fortuitously the ACR and also recently developed new criteria for rheumatoid arthritis remission and so I’d ask you here which of the following is true.

Anybody – SED number 3, number 3 is indeed the correct answer. And it’s really a composite of physician and patient assessments of disease activity. It really isn’t based on what a patient thinks remission should be. It’s really based more on how they feel at that moment in time and I’ll try to
make that distinction as I walk through this and see – as we’ve analyzed some of the data that we have. And so Aarat took an interest in this and he’s put together a study related to this concept and so what he really wanted to do is ask the question – if patients are in this new, meet this new remission criteria, do they indeed have a good quality of life or productivity? And what he wanted to do was make the case that if you compare them to people who have low disease activity, that even, that remission is even better than getting people almost to remission. So one of the things that I have always done as a doctor is as I’ve treated these folks and I’ve gotten them down almost near remission, I’ve had to think about whether I want to go further with my drug therapy or not. What should the ultimate target be? Obviously this is an individualized question, you have to make an assessment of how the patient feels about this as well. But at the end of the day, you know, we never really had much in the way of data to suggest to us whether getting the low disease activity was enough. Because the decision that is involved in moving from low to remission, oftentimes is going to involve more risk to the patient and usually will involve additional therapies that will put the patient at additional risk. It will also involve additional cost and more effort on the patient in terms of taking medication.

So the underpinnings for this once again is that ACR and EULAR propose these new criteria, they were primarily developed for use in clinical trials. It’s really unclear whether or not these remission criteria are useful for the usual care of rheumatoid arthritis patients and it’s also unclear whether or not remission itself is associated with a good outcome and an acceptable quality of life for patients.
So what are the new remission criteria? Well they’re pretty stringent so – I talked to you a little bit about disease activity scores a few moments ago. For you to be in these new, to be in remission as defined by these new criteria, you have to have a tender joint count, swollen joint count, CRP and a patient global health, each one of these individually has to be 1 or less. Actually for those of you who care for patients, you know, you think about how many of your patients are actually this well controlled.

And a comparable index, the SDAI which I talked to you about earlier, a score of a 3.3 was also tested when this committee put these together, these criteria together and this was found to be acceptable, so you could meet either one of these or both.

So the first thing that Aarat did was he asked the question, if you are in - depending on your disease activity what does your quality of life look like? And so he found that for patients in these different categories of disease activity as measured by the DAS28 that there was a significant difference in the quality of life, this is the physical component of the measurement of quality of life. Between those who were in DAS remission which is this right here, not ACR/EULAR but rather DAS remission, compared for example to those who are in high disease activity also in low and moderate disease activity and because the SF12 which is the quality of life instrument that we’re using here has published norms, we put the norm for patients in our study, it would be comparable to patients in our study. And so you can see that patients in remission at least by DAS28 definition do not quite
meet the norm for having a quality of life similar to people in that norm group. But we can’t do stats on this just because of the nature of the data.

And so he also found that there was an impairment in work productivity in these individuals. The higher your level of disease activity, the more you were impaired using this work productivity instrument as well. And he also found that functionally using the RAPID3 that people in high disease activity for example based on the DAS had quite a bit worse functioning as it related to the RAPID3. And I point out that in contrast to the SF12 which I showed you two slides ago, the RAPID3 and the work productivity as they get worse they get higher whereas the SF12 gets – is just the opposite.

Okay and so as part of this analysis what he found is that in our cohort approximately 18 percent of the cohort were in remission as defined by ACR/EULAR. And he found that those, that the mean SF12 scores, if you were in this more rigorous definition of remission than the DAS28, were very similar to what they would be for an age matched normal population.

What he also found is that this other instrument that we use the CDAI, when you used it’s remission criteria it was actually very comparable to the remission criteria for ACR/EULAR. And these folks had comparable SF12, work productivity and RAPID3 scores. Whereas in contrast the criteria that had been used and these were actually the criteria that were most used by rheumatologists worldwide for defining remission prior to this, people thought of remission on the basis of the DAS28 but
actually the ACR/EULAR definition of remission was much more stringent then the DAS28 remission criteria. So this is the difference in terms of the number of people in those different groups.

So what he found was that – that individuals when you compared people who are in ACR/EULAR remission and you compare them to the people who are in DAS28 remission but not ACR/EULAR remission, in other words this is the fraction of people who are slightly above the remission criteria, we expected that these people would actually, probably have a comparable quality of life as people in remission by ACR and what he actually found is that their quality of life was actually significantly worse especially in the physical component score. And what we’re talking about here for those of you that understand DAS scores, is that remission in DAS is defined as a 2.6 and really what, and so what these people represent here is that because the ACR/EULAR remission criteria are comparable to probably a DAS of around 2, we’re talking about a very small difference between a 2 and 2.6 on the DAS having a relatively I think very profound effect on the quality of life for these patients.

They also had significantly lower work productivity and they also had significantly worse function based on that. And as you might expect when you compared the remission, people in remission to higher levels of disease activity, low based on the DAS or even the CDAI. They also had a worse quality of life, work productivity and function as well.
The other interesting thing about all this is because we have a lot of medication data on our patients, he was able to show that interestingly when you compare these groups and right here what we’ve done is I’ve given to you as a comparison of the CDAI. Remember CDAI remission is almost equal to ACR/EULAR remission. When you look at this remission category they’re actually using about the same amount of biologics and DMARDs as all the other groups. But what they’re using a whole lot less of are corticosteroids and especially opiates. And so this does, this lends at least support to the idea that these people are actually a whole lot better because they’re using a lot less of these additional drugs to kind of prop up so to speak these drugs over here.

So once again our conclusion for this anyway was that the subjects in ACR/EULAR remission and also once again CDAI remission would be equivalent here, had a quality of life, functional ability and work productivity that were similar to age matched norms suggesting that these new remission criteria represents remission from the patient and the physician perspective.

And that we also suggest to you that the DAS28 definition of remission is not comparable. And since there was this discrepancy between the groups and overall our data supports the idea that the CDAI represents a good instrument to use in the context of our studies that we’re doing here for a variety of reasons.

And then the medication data that I showed you suggests that for patients to move from low disease activity into remission, it’s going to actually require that they actually use greater use potentially of
combination immunosuppressive therapies. So once again will that be what every patient needs or wants. That’s very much of an open question and that really hasn’t been decided by any of this research. This really emphasized to me that when the opportunity exists, when the patient is interested, I’m working much harder these days based on this data to push people into remission to give them that opportunity to have that better quality of life.

So let me summarize all of this and then tell you a little bit about where we’re going with this. So the summary from this is that I believe that there’s a strong rationale for real world studies of rheumatoid arthritis patients based on the recommendations of the Institute of Medicine and supported by our comparisons of the RACER registry to randomize control trials. We believe that both the ’87 ACR and the new ACR/EULAR RA diagnostic criteria are valuable for characterizing patients in usual care settings and we’re using both of them.

We think that the CDAI is the preferred instrument at least for following disease activity versus the DAS28 and this patient reported outcome the RAPID3. I want to point out that I do believe the RAPID3 is valuable, we continue to do and we will continue to do it. I’m mostly interested in the functional aspects of what it measures so we’re going to continue that. And then ACR/EULAR and CDAI defined remission are associated with the quality of life comparable to age-matched normal subjects. And I think that echoing some of the recommendations that were made by that international task force, that this is the ideal goal. I really probably should have put in the ideal here for most rheumatoid arthritis patients. So once again your decisions as you talk to your patient about what to
do are going to be based on their own interests as well and their risk, their willingness to take risk as it were.

So where are we going with this? I’ll stop after this and ask questions. One of the things that we’re very interested in and Aarat has made some real nice progress on is using electronic search criteria to expand the number of patients that we’re studying. I mentioned to you earlier that it was our belief that there’s approximately 2600 or so rheumatoid patients in our system. This is actually based on a recursive portioning algorithm that Aarat created in conjunction with Steve Wiesneski and this has, this search algorithm has a 95 percent sensitivity and 96 percent specificity in terms of identifying patients just from electronic criteria based on what Aarat’s done. So we’re really hoping that that’s not only in addition to the patient reported outcomes that we’re collecting in RACER but we can also use the medical records to expand what we’re doing using the valuable information here.

And then we’ve also upgraded our system now. We’ve over the summer expanded the RACER system to allow for web-based data entry. We think this is going to be really important because it will allow patients to actually access the system from home and potentially complete this questionnaires in advance of their appointments.

We’ve also initiated a comparative effectiveness study, we just got final approval for this yesterday from the IRB, I refer to this study as TEZLA and what we’re going to do is look at a comparison between some of the different drugs that we use for patients that have not responded adequately to
their first biologic therapy. So there’s a whole lot of unknowns about what do you do after somebody
does not respond to a therapy. And so as we move forward this will be the next thing, next piece of
information that we’ll have.

And then this other thing which I’ve just recently taken to calling AZCARI, is that we really want to
be able to move RACER from research to standard of care and so what we’re about to start and
we’ve also gotten approval for this just in the past month or so, to move forward with this. Is that we
want to do a treat to target type strategy for assessing whether or treat to target is really a valuable
tool that should be used in a setting of usual care settings or not. Because all of the previous studies
that have been done in this area have all been run more like clinical trials rather than usual care.