UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

+ + +

VIRTUAL PUBLIC MEETING - ORTHOPEDIC STRATEGICALLY COORDINATED REGISTRY NETWORK (ORTHO CRN)

+ + +

November 4, 2021
9:00 a.m.

Via Videoconference

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

MEETING PARTICIPANTS:

CAPT RAQUEL PEAT, Ph.D., M.P.H.
Director, Office of Health Technology 6
Office of Product Evaluation and Quality
CDRH/FDA

DANICA MARINAC-DABIC, M.D., Ph.D.
Associate Director, Office of Clinical Evidence and Analysis
Office of Product Evaluation and Quality
CDRH/FDA

ART SEDRAKYAN, M.D., Ph.D.
Professor, Weill Cornell Medical College
MDEpiNet Project, FDA

VINCENT DEVLIN, M.D.
Chief Medical Officer, Office of Health Technology 6
Office of Product Evaluation and Quality
CDRH/FDA

JANINE AUSTIN CLAYTON, M.D.
Associate Director for Research on Women's Health
Director, Office of Research on Women's Health
National Institutes of Health

HONGYING JIANG, Ph.D., R.A.C.
Safety Signal Manager, Office of Health Technology 6
Office of Product Evaluation and Quality
CDRH/FDA

AMANDA CHEN, M.S.
Doctoral Student, Harvard University

SUVEKSHYA ARYAL, M.P.H.
Senior Research Analyst, Department of Population Health Services
Weill Cornell Medicine

JOHN BOWSHER, Ph.D.
Master Reviewer, Office of Health Technology 6
Office of Product Evaluation and Quality
CDRH/FDA

DIANE SMITH, Ph.D.
Chemist Staff Fellow, Office of Health Technology 6
Office of Product Evaluation and Quality
CDRH/FDA

YELIZAVETA TOROSYAN, M.D., Ph.D.
General Health Scientist, Office of Clinical Evidence and Analysis
Office of Product Evaluation and Quality
CDRH/FDA

PAUL VOORHORST, M.S., M.B.A.
V.P., Clinical Science and External Research
DePuy Synthes

BRENT SHOWALTER, Ph.D.
Assistant Director, Office of Health Technology 6B
Office of Product Evaluation and Quality
CDRH/FDA

ELIZABETH PAXTON, Ph.D., M.A.
Director, National Implant Registry Program, U.S.
Kaiser Permanente

MICHELLE MARKS, P.T., M.A.
Executive Director
Setting Scoliosis Straight

VAHAN SIMONYAN, M.S., Ph.D.
Senior Director of Bioinformatics, CRISPR Therapeutics
Chief Scientist, WHISE Consortium
Professor, George Washington University

BILAL CHUGHTAI, M.D.
Associate Professor of Urology
Cornell University

A. NOELLE LARSON, M.D.
Associate Professor of Orthopedics
Director of Research, Division of Pediatric Orthopedics and Scoliosis
Orthopaedic Surgeon, Mayo Clinic

CAPT JONATHAN FORSBERG, M.D., Ph.D.
Orthopedic Oncologist, Clinical Scientist
Murtha Cancer Center, National Cancer Institute, Johns Hopkins University

JIALIN MAO, M.D.
Assistant Professor, Department of Population Health Sciences
Weill Cornell Medicine

PER-HENRIK RANDSBORG, M.D., Ph.D.
Orthopedic Surgeon, Akershus University Hospital (Norway)
Researcher, Hospital for Special Surgery
Associate Professor, Weill Cornell Medical College

FLORA SANDRA SIAMI, M.P.H.
Senior Vice President
National Evaluation System for health Technology Coordinating Center

ROBERT NELISSEN, M.D., Ph.D.
Professor, Department Chair, Leiden University Medical Center
Medical Delta Professor, Department of Bioengineering
Delft University of Technology

DANIEL CAÑOS, Ph.D., M.P.H.
Director, Office of Clinical Evidence and Analysis
Office of Product Evaluation and Quality
CDRH/FDA

INDEX

INDEX

INDEX

M E E T I N G

(9:00 a.m.)

CAPT PEAT: Good morning, and welcome to the fourth annual Orthopedic Coordinated Registry Network, or Ortho CRN meeting. My name is CAPT Raquel Peat, Director of the Office of Health Technology 6, which is the Office of Orthopedic Devices at FDA Center for Devices and Radiological Health. Our office is committed to advancing innovative medical devices for treatment of orthopedic patients, in addition to addressing COVID-19 workload to help bring diagnostic devices, personal protective equipment, and therapeutics to patients as quickly as possible.

While in the midst of the pandemic, it has enhanced a focus on real-world data sources, which require building an advanced medical device ecosystem and national infrastructure for faster, better and less costly evidence generation for orthopedic technologies. By way of history, the Center established in 2017, following the successes of International Consortium of Orthopaedic Registries, the Medical Device Epidemiology Network, MDEpiNet, a partnership between academia, FDA, industry, patient groups, professional societies, providers and other medical device stakeholders, launched the Ortho CRN to continue to promote the development of systematic collaboration among existing national orthopedic registries, clean databases and other data sources.

Through annual meetings such as this, the vision of maturation, achievement of crucial milestones and stronger partnership among Orthopedic Strategically Coordinated Registry Network (Ortho CRN), was championed and continues to foster communication, engagement and collaboration among all stakeholders in the orthopedic community, and focus on efforts to streamline and enhance the premarket and postmarket evaluation of the safety and effectiveness of orthopedic devices.

Our last Ortho CRN meeting was held on November 2nd, 2020. That meeting was

centered on supporting changes regarding real-world evidence and the collection of such evidence. We achieved the objectives of that meeting by providing an update on the National Evaluation System for Health Technology coordinating center, otherwise called NESTcc, with an overview on the NESTcc orthopedic test cases, impact of the Ortho CRN in developing existing registries, and evidence generation, and ended the day with a discussion on capitalizing on digital solutions and novel methods.

From that meeting, we had a number of actionable steps from the identified gaps in our orthopedic ecosystem that we embarked on addressing in the past 12 months. For example, first, inclusion of patients in the development and implementation of real-world evidence generation of data; two, additional emphasis on the inclusion of patient-reported outcomes in clinical studies while collaborating with others on understanding the limitation of interpretation, standardization that includes consistent demographic data that highlights health disparities, sex/gender stratification, and risk outcomes; three, utilizing real-world evidence with a reasonable sample size to aid in development of useful buckets of diagnosis in certain areas of orthopedic; four, researching the role of artificial intelligence in medical imaging, more information on mobile applications, such as high performance, integrated virtual environment platform, and lastly, more dialogue on inclusion of imaging in real-world evidence, and how we can determine next steps in providing valid scientific evidence to support safety and effectiveness.

Today we will discuss topics of real-world evidence, patient-centered outcomes, and international and disparity research. You will hear more on real-world evidence research, various orthopedic patient-reported outcomes and patient preference projects, and national and international collaborations.

I would like to acknowledge and thank the entire FDA team, including staff from CDRH's Office of Orthopedic Devices, the Office of Clinical Evidence and Analysis, and the

Office of Communication and Education and other FDA contributors. In addition, we are grateful for the contributions of our external collaborators, the Ortho CRN community, and the EpiNet and Cornell for all that you continue to do, and note that these kind of partnerships are exactly what the Center is fostering across each device-specific portfolio. And we greatly appreciate your attendance and participation in today's meeting.

I will now turn to our Master of Ceremony for today's meeting, Dr. Danica Marinac-Dabic, who is the Associate Director of the Office of Clinical Evidence and Analysis, Office of Product Evaluation and Quality here at FDA Center for Devices and Radiological Health. Prior to this position, she was the Director of CDRH's Division of Epidemiology. Under her leadership, in 2010, the MDEpiNet initiative was launched, and led to the development of numerous international registry collaborative efforts, including development of the International Consortium of Orthopaedic Registries Initiative, International Consortium of Cardiac Registry, and the International Consortium of Vascular Registries.

Thank you, Dr. Dabic, for your willingness again to participate as M.C. for today's event, and I will turn the meeting over to her. Thank you, and enjoy the rest of the meeting.

DR. MARINAC-DABIC: Thank you. Thank you, CAPT Peat. And good morning, and welcome to our annual meeting of the Orthopedic Strategically Coordinated Registry Network, also known as Ortho CRN. I am delighted to welcome close to 200 colleagues from the national and international orthopedic ecosystem. Your active participation, your continued leadership, and continued work with us are truly, truly appreciated.

Today's conference is designed to continue to advance our strategic dialogue, and also our practical approaches for all Ortho CRN stakeholders, and serve also as a catalyst for further engagement to promote innovation of orthopedic medical devices. This conference be also the series of collaborative achievements over the past decade, including as CAPT

Peat mentioned, our International Consortium of Orthopaedic Registries that was launched back in 2010, that actually pioneered an unprecedented international harmonization, and also executed a series of distributed analyses across international registries. That effort, and those achievements have inspired the growth of Ortho CRN, and continue to capitalize on the developments today, both international and international real-world evidence cooperations.

Some of the logistics remarks that I would like to start with. Each session today will be chaired by two co-moderators. I will introduce all moderators and speakers for continuity of the flow of the conference. Speakers and panelists are encouraged to bring normal ideas and to be provocative. Today's the day to actually bring about new ideas of how we can better work together in the future.

Each speaker today will have up to 10 minutes to give the presentation, followed by moderated discussion at the end of the sessions. In addition, we would also like to hear from you, our audience and our participants that are actually joining virtually today. Please use the link that will be showed on the screen throughout the meeting to comment and send your questions for our panelists and moderators. Designated staff will monitor your comments and questions throughout the day. And if we are not able to address all of them during the discussions, any of those unanswered questions or comments will be saved and addressed later.

We will also have short breaks, approximately 10 minutes between the sessions or the segments of the sessions, depending on the length of each session. And then we will also have a 60-minute break for lunch. So let's begin our program.

The first session today will focus on the real-world evidence research, and will be moderated by our two distinguished federal leaders from FDA and NIH. First CAPT Raquel Peat, who is our Director of CDRH's Office of Orthopedic Devices, and Dr. Janine Clayton,

who is an Associate Director of NIH's Office of Research in Women's Health. This session is, as you saw from the agenda, relatively long, and that's why we divided it into two sections, comprising of presentations followed by moderated discussion.

In the first section of this session, we will hear from five speakers. Our first speaker is Dr. Hongying Jiang, a Safety Signal Manager at the CDRH's Office of Orthopedic Devices, and she will introduce the topic of sex/gender diversity in orthopedic clinical trials.

DR. JIANG: Good morning, everyone. My name is Hongying Helen Jiang, a health scientist, and a Safety Signal Manager in OHT 6. Today I would like to present our preliminary results about sex/gender diversity research in orthopedic device clinical trials on behalf of our OHT 6 team, Drs. Kate Kavlock, Panox, and CAPT Raquel Peat. Next slide please.

There are known racial and sexual disparities in health, such as higher incidence and severity of disease conditions like diabetes, cancer and recent COVID-19 in some minority groups. These differences affect our FDA's regulatory decisions, such as requirement of post-approval study (PAS), labeling update, and even affect how we communicate to the public in FDA's Letter to Healthcare Providers and safety communications.

In 2010, we issued the FDA Safety and Innovation ACT (FDASIA), recommending inclusion of demographic subgroups in clinical trials. In 2014, FDA issued another guidance document, to promote study enrollment and data analysis accounting for sex and other demographics. In this guidance, one orthopedic example is used. Do you know what it is? It's a summary of metal on metal (MOM) total heat replacement and heat resurfacing studies. The revision rate was higher among women 3 to 5 years post implantation than men in most of those studies, specifically 2.7 to 19.8% versus 0 to 14.6%. Next one, please.

Therefore, we've collected baseline demographics from clinical trials in all OHT 6 approved PMA, HDE and de novo submissions. Then we've conducted descriptive analysis,

including various counts calculating, minimum, median, mean, maximum and percentages of the study subjects in any study arm for each subgroup. Today's presentation is focused on sex/gender differences in the study enrollment.

Next, I would like to show you some of our preliminary results. Figure 1 is a flow chart that shows the stats we've taken to reach the final data set. There are a total of 94 PMAs, HDEs and De Novos. Each submission my have more than one cohort or trial, for example, an HDE -- sorry, an IDE cohort and a continued X cohort. Therefore, we've collected a total of 254 records or cohorts.

For today's presentation, we are focusing on analyzing the investigational device arm that has more than 30 patients, which means 128, and 17 cohorts were excluded. This left us with a total of 109 studies or cohorts. A quick breakdown among three of our divisions, Division A, B and C had 37, 34 and 38 studies, respectively. Next, please.

In the final 109 device groups, we've included a total of 22,000 patients. The median enrollment was 151 patients for per study group. Within total studies, most studies, 103 were PMAs, 5 were HDEs and only 1 was De Novo. In terms of sex distribution in the enrollment, let's first look at the overall female enrollment in a total enrollment. For Division A, arthroplasty devices, the overall female enrollment is relatively low, 34%. Then Division B, spinal devices had 48%, and Division C, restorative, repair and trauma devices had the highest, 51%. The enrolled female subjects in the total subjects are also included in the parenthesis. Next, please.

Let's look at Division A's trials in more details. Among all 38 trials, the median, half of the trials enrolled 76 subjects, but the minimum number of female enrolled was only 19, very low. Figure 2 shows the average female enrollment percentages in arthroplasty devices, grouped by six device types. X axis represent the percentages, Y represent the six groups included in parenthesis, with the number of studies, reported sex enrollment over

the total study per device type. For example, the shock wave generator for pain relief devices, there were a total of nine studies, but only six of them reported female enrollment, therefore six over nine on the figure.

From this figure, we can see that the enrollment percentages are very broad, from 25 to almost 100% in finger arthroplasty. Does it mean that female use the fingers more often than males, and more prone to injuries? Since there's only limited, one or two clinical trials for some device types, it is hard to conclude if these percentages are a true reflection of the real-world usage of those devices, per different device types. Next, please.

Same type of figure. Let's look at the average female enrollment percentages in spinal devices, grouped by five device types. From this figure, we can see that the top two types had average enrollment around 40%. The middle two were 50%, but the last two, IS, idiopathic scoliosis correction devices, had the highest, 88%, which we believe reflects the fact that female enrollment, female patients are predominant sex in the real-world usage. The overall percentages is around 51%, which is pretty even between the two sexes, and it ranged from 38% to 89%. Next, please.

This figure is the average female enrollment percentages in Division C's devices, grouped by six device types. From this figure, we can see that the top four device types had around even enrollment between the two sexes, but the hyaluronic acid trials had a 63% female enrollment. And the only one MTP, metatarsal phalangeal cartilage replacement had the highest, 80% of female enrollment. Again, there are some device types only had one or less than four trials, therefore limited conclusions can be drawn. Next, please.

In summary, from the above preliminary analysis, we can see that there are enrollment differences in sex gender in orthopedic device trials. Specifically, female enrollment ranged from 19 to 420 subjects per trial, and accounted for 25 to 98% of the total enrollment. This is very broad, and appears to be broader and higher than other, such

as some groups of cardiovascular devices that had overall consistent lower than 40% female enrollment. Some of those differences appear to be related to the underlying disease distributions in different subgroups. However, some may not be due to the limitations in our studies and data collection. Additional investigation is warranted, to identify other disparities and challenges in enrolling underrepresented patient populations. Next, please.

Thank you for your attention. This ends my presentation.

DR. MARINAC-DABIC: Thank you, Dr. Jiang, for an excellent presentation. Now it's my great pleasure to introduce Amanda Chen, who used to be a fellow with an M.S. at Weill Cornell University, and now is a doctorate student at Harvard, who will be talking about the study of the cooperative, the actual results of the cooperative study on sex/gender differences in hip replacement.

MS. CHEN: Good morning. On behalf of our team of collaborators from Weill Cornell Medicine, Kaiser Permanente and the FDA, I'm pleased to present our research on the association of sex with risk of two-year revision for patients who are undergoing total hip arthroplasty. This study was funded by the FDA, and the grant information is available here.

To start with some background on the subject, we know that total hip arthroplasty is a common and effective elective procedure for the treatment of end stage osteoarthritis, a leading cause of disability. We also know that the world population is aging, and includes more females than males, with higher rates of THA utilization among females. Additionally, current evidence of sex disparities from prior studies is limited, and the importance of sex as a risk factor for revision surgery is unclear. There are some studies which suggest an increased risk of revision associated with the male sex, while others suggest an increased risk associated with the female sex, or no risk difference between males and females.

The primary objective of the study is to evaluate the association between sex and

two-year revision after THA. A secondary objective of the study is to identify fact modifiers for the association between sex and all-cause revision. This study was an observational cohort study with data from the New York State Department of Health Statewide Planning and Research Cooperative System, as well as the California Office of Statewide Health Planning and Development data from 2015 to 2018.

Our study population includes 100,000 osteoarthritis patients who underwent primary THA in New York and California. The main outcome measure was all-cause revision, defined as the removal, replacement or addition of one or more implants performed on the same side of the hip as the index THA.

For variables included in our study, we had demographic information, including age, which was grouped into age categories for under 55, 55 to 64, and greater than 65, sex, race, which included white, black, Hispanic or other, insurance type, which included Medicare, Medicaid, commercial, self-pay and other, state, and comorbidities, which include morbid obesity, hypertension, COPD, congestive heart failure, diabetes, depression, peripheral vascular disease, coagulopathy, hypothyroidism, valvular disease, renal disease, cancer, and hypocholesteremia, as well as facility mean annual volume.

For our statistical methods, we used Kaplan-Meier analysis to analyze the cumulative incidence of revision by sex, and Cox proportional hazard regressions to examine the impact of sex on revision rate. The models included sex as the sole explanatory variable, as well as adjustment for demographic and clinical characteristics.

This table depicts our patient characteristics, and we can note that our cohort was majority female, and the average age of the cohort was 65.9 years, with females older than males. The majority of patients were white race, Medicare beneficiaries, and for comorbid conditions, 14.2% of females had depression compared to 6.9% of males, and 20.3% of females had hypothyroidism, compared to 6.5% of males.

This Kaplan-Meier plot of revision event in THA by sex shows that females had a higher all-cause revision rate compared to males. The 2-year revision rate was 2.5% in females, and 2.1% in males.

We performed three method Cox models. The first model included sex as the sole explanatory variable. In this unadjusted Cox model, the hazard of all-cause revision was 22% higher among females compared to that in males. Our second model adjusted for age, race and ethnicity, insurance status and facility mean annual volume. After adjusting for these demographic characteristics and facility mean annual volume, the hazard of revision was 20% higher among females, compared to males. In our third models, we added comorbidities into the model, and we found that females maintained a 16% higher hazard of revision.

We also looked at septic revision as an outcome measure, and found that in both the unadjusted as well as adjusted models, the hazard of revision was lower among females compared to that in males. We additionally performed subgroup analysis for the group of individuals less than age 55, as well as those shaded in low-volume centers.

This figure shows the 1 and 2-year estimated sex specific all-cause revision rates by age as well as facility and volume. Panels A and C on the left-hand side show the 1-year rates, while Panels B and D on the right-hand side show the 2-year rates in our fully adjusted models, with the blue line indicating females and red line indicating males. These figures show that the revision rates significantly differed among females and males in our attraction analysis at both 1 and 2 years.

We performed stratified analysis which showed that females had a higher risk of revision than males if they were under 55 years old, were white, had Medicare or commercial insurance, or were treated at a low-volume facility. There was no difference in revision rates among patients who were black or Hispanic, had Medicaid insurance, or had

the index procedure at a high-volume facility.

Our study found that after adjusting for demographic characteristics, patient comorbidities and facility volume, there was minimal clinically meaningful difference between males and females. While we did find that females had a slightly higher risk of revision compared to males overall, both sexes had low baseline revision risk. The absolute difference was minimized with tighter covariate adjustment in our models.

Additionally, compared to males of the same age, females under 55 years old had a modest increase in all-cause revision rate, suggesting a weak signal. These findings suggest that there is no clinically meaningful difference in all-cause revision rates between males and females at 2 years follow-up. The very modest difference in the subgroup of patients who were under 55 requires future study. Thank you for your time.

DR. MARINAC-DABIC: Thank you, Ms. Chen. That was very informative presentation that I'm sure we're going to hear much more during discussion.

Now, I would like to introduce Suvu Aryal, who is the Director of the MDEpiNet Operations at Weill Cornell Medicine. She is going to move us to the area of knee replacements, with a comparatory study that was done Ortho CRN team.

MS. ARYAL: Good morning, everyone. My name is Suvu Aryal, and today I'm going to present our study on sex differences and risk of revision in total knee arthroplasty. The study was conducted at Weill Cornell Medicine by MDEpiNet Ortho CRN team, and you can see the co-authors of the study on the screen. This is our disclosure.

I'll briefly go over the background of this topic. A total knee arthroplasty is a common procedure in osteoarthritis. It's performed in over 700,000 patients annually in the U.S. More than 12 million people are living with a knee replacement in the U.S. and the number is projected to grow substantially in the coming decade. To note, females account for more than 60% of the procedures.

There are known differences in TKA. Females suffer from worse osteoarthritis. They also suffer from worse preoperating functional scores and disabilities. They experience higher rates of obesity, post-operating transfusion and longer hospital stay compared to males. Conversely, males are at a higher risk of multiple adverse events, including increased operative time, cardiac arrest and (indiscernible) readmission. They also have higher rates of post-operative wound infection, surgical site infection when compared to females.

There is a mixed evidence of sex as a risk factor in revisional TKA, sometimes showing similar effect, and some studies showing higher risk in males. The existing evidence has the limitations in terms of generalized ability, and use of older data, as well as they use older procedure codes, ICD-9, that don't differentiate operating site, or lateral or knee.

So, with the known background of TKA, our objective in the study was to study the association between sex and 2-year revision, specifically all-cause revision, septic revision and aseptic revision in primary TKA. And our secondary objective was to investigate subgroup effects in age, race, insurance, facility volume in association between sex and revision.

So, we conducted an observational cohort study, utilizing New York SPARCS data from 2016 to 2018, and California OSPHD data from 2015 to 2017. Our subjects were adult population who underwent TKA in New York and California. And our outcomes of interest were all-cause revision, which is defined as removal or replacement of any implant component or an entire implant, septic revision, revision events with concurrent (indiscernible) infection diagnostic codes, and aseptic revision, revision events without concurrent diagnostic infection.

We looked at demographic variables of age, race, insurance and state, and

comorbidities like morbid obesity, hypertension, COPD, congestive heart failure, diabetes, depression and others listed here, as well as (indiscernible) volume. For statistical methods, we used Kaplan-Meier analysis of all-cause, septic and aseptic revision and compared using log rank test. We also used Cox proportional hazard models to study the sex differences. First we asked, does sex difference exist in risk of revision, so as to study overall sex differences by adjusting for covariant, and secondly we asked whether true interaction exists between sex and other variables in risk of revision, to study sex differences in those subgroups.

This table shows the patient characteristics in our data. We had 212,385 patients. Of those, 62% were females, 62% were over the age of 65 and 68% were white. You can also see that 55, about 55% had Medicare insurance. In regards to comorbidities, we found that diabetes were slightly higher in males, and obesity was slightly higher in females, whereas to note, depression and hypothyroidism were significantly higher in females.

These are the Kaplan-Meier analysis graphs. In orange line, you will see male data and male trend, and of the blue line for female. Overall, all-cause revision, all-cause risk of revision was slightly higher in males, compared to females, 2.2 versus 1.7. We further looked at aseptic and septic - septic and aseptic revision, and we found that septic risk of revision was higher in males than females, but there were no significant differences in aseptic revision, and these are the 2-year rates of revision in males and females.

Further, we conducted hazard analysis to study the sex differences in an adjusted model. We found that males had 32% higher rates of all-cause revision and 97% higher rates of septic revision. And at the bottom row you can see that aseptic revision was not significantly different between males and females.

Moving on with our secondary analysis, I do note that we checked for (indiscernible) modification by age, race, facility volume and insurance. Since all of them showed some

kind of interaction, we did stratify the analysis. So, this shows sex differences in age subgroups. We can see that the younger patients are most vulnerable for risk of revision, especially younger males. Similar results are seen with all-cause revision and septic revision.

And finally, this slide shows the subgroup analysis for race, insurance and facility volume, and of course, plotted we see that all the subgroups, for all the subgroups, males tend to have higher risk of all-cause revision, and septic revision, all-cause revision on the left-hand side and septic on the right. Interaction was significant mostly for white patients, patients who had insurance and commercial - Medicare and commercial insurance for both all-cause and septic.

So finally, in conclusion, we found that males had slightly higher risk of all-cause revision in TKA than females, at 2 years, but this can be potentially explained by higher risk of septic revision in males, because aseptic revision is not significantly different. As well, we found that younger patients were at higher risk of revision, and the sex difference was more prominent in younger patients, suggesting that younger males may be at a higher risk than females in TKA, and this needs further research.

Some of the strengths and limitations of our study. Strengths are that we used the most up-to-date administrative cohort data available. We had a large, analyzable cohort from two large states, from New York and California, which covers 20 percent of this population. We used the most up-to-date codes, ICD-10 to distinguish laterality. And in terms of limitation, usually codes have some coding errors. You know, we were unable to distinguish implant design, surgical approach and reason for revision. And finally, it was limited to a shorter-term follow-up because we used ICD-10 codes, which became available after October 2015.

These are our references that we used in this paper. And with that, I'd like to thank

the Cornell and FDA study team for their contribution to the study, and to Ortho CRN community members for this opportunity to present. Thank you again, and I look forward to the discussion.

DR. MARINAC-DABIC: Thank you. Thank you, Ms. Aryal, and thank you, the entire Cornell team indeed for this state-of-the-art epidemiologic analysis, with a number of things that were pointed out. Thank you indeed.

Now, with a great honor, I would like to now introduce my colleagues from FDA, that will actually take a deeper dive, moving us from the epidemiologic analysis to in fact the studies of genomics and genetics identifying gene frequencies that are associated with early joint failure of orthopedic devices in women. We're going to hear from two presenters, Drs. John Bowsher and Diane Smith, both biomedical engineers, scientists, and master reviewers at the Office of Orthopedic Devices at CDRH.

DR. SMITH: Good morning, everyone. My name is Dr. Diane Smith. My colleague and I, Dr. John Bowsher, are going to discuss identifying gene frequencies that are associated with early joint failure of orthopedic devices in women. Thank you for the opportunity to speak with you this morning.

DR. BOWSHER: So, to help advance personalized healthcare, our goal is that in the near future, an orthopedic surgeon will not just consult patient stats and imaging prior to implanting a total hip or total knee, et cetera, but will also investigate your genes. And the reason for this is because your genes strongly influence how your body will respond to an orthopedic device, without you even knowing about it.

All types of artificial joints, hip, knee, et cetera, release wear particles and ions during use. It's just simply inevitable. And how your body reacts to these implant particles and ions is governed by your immune system, and your immune system is governed by your genes. So, your genes can be an important part in your device failure without you even

knowing about it. This is similar to a person's response to COVID-19. Again, it's highly dependent on your genes.

While large amounts of wear debris can cause adverse tissue reactions for most patients, we're more interested in a subset of patients that have low-wearing devices, especially cobalt chrome devices. And they still go on to produce a delayed hypersensitivity reaction. And we believe these patients are genetically predisposed to a delayed metal sensitivity, and we may be setting them up for premature failure by giving them a cobalt chrome wearing device.

We believe that in the near future, these patients can be easily identified by screening with their genes, allowing surgeons and patients to make better informed clinical decisions, improve target patient follow-up, or to simply contraindicate certain cobalt chrome-containing orthopedic devices for certain gene frequency types.

So, when you look at the causes of revision surgery of orthopedic devices in general, like when you see registry data, you see many common causes. Some are mechanical or device-related, such as fracture, dislocation migration, et cetera. And some are patient-related failure mechanisms, like pain, lysis loosening or osteolysis, or adverse reactions to metal debris, or sometimes called ALTR, or infection.

I think what's interesting is when you look at these failure curves, what you don't see is that the patient's genes and their immune system were contributing factors in these curves. Another way to think about a wearing orthopedic implant is as it's like a liver transplant. Your body will eventually reject it over time in some way. Like with liver transplants, surgeons match this transplant to the patient using genetic information to maximize its longevity, and we now believe that this is a legitimate method of how we should be thinking about orthopedic devices.

Metal sensitivity is thought to be much more involved now in joint failure than we

previously thought and is only now being fully explored in detail. We hear from multiple sources that women have worse functional outcomes in joint replacements than men, and this is thought to be caused, that women appear to respond more aggressively to implant wear debris than males, such as cobalt chrome. To address this issue, the FDA held a panel meeting at the end of 2019, where it was discussed that there is no method of prescreening women that are high-risk for delayed type metal sensitivity reactions to cobalt chrome as a precursor for implant failure, and this is representing a significant unmet need.

So, this slide highlights the problem that we are faced with the unpredictability of adverse reactions to metal debris, as well as highlighting just simply the challenges that we face in better predicting clinical outcomes in patients with metallic orthopedic devices. So, the patient that you see on the left is a patient that had a low blood cobalt level, yet presented with worse groin pain, and at revision surgery, this patient had a large (indiscernible) fluid effusion, and extensive soft tissue necrosis.

In contrast, the patient on the right was an active patient and experienced minimal pain yet presented cobalt levels that were 150 times higher than the patient on the left and showed no metal sensitivity and no tissue damage. The tissues were still viable yet showing metallosis. However, as you can see, these reactions are very different for these two patients.

DR. SMITH: To begin understanding the unpredictable nature of these failures, I started investigating taper and bearing surface wear analysis. This is research that the FDA sponsored, and once we started matching the total amount of wear to clinical outcomes, we started understanding the relationship between wear and ALVAL. To understand wear mechanically, the devices were producing wear. We can't understand this problem without the context of the device wear. Eventually, we began watching wear to tissue analysis, implant failures and genetic information, where we noticed that high-risk genes were

associated with metal implant failure due to ALVAL, even in the absence of high wear.

In collaboration with FDA, beginning in 2008, Dr. Langton started noticing that higher metal wear led to higher failure due to ALVAL, but realized that this was not the entire picture. The curves represent survivorship of metal-on-metal hip implants with respect to time after implantation. Cobalt blood ion levels of 2 to 4 mcg per liter are relevant to both hip and knee clinically relevant wear rates. Notice that the implants in females, represented by purple, green and bright blue curves, show lower rates of survivorship as time goes on.

The curves that you see on the screen represent survivorship of hip implants with respect to time in years after implantation. Survivorship of 1 means that there were no failures, whereas a survivorship of 0 means that 100% of the implants failed. The failures shown here are due to the development of ALVAL. These curves show survivorship of implants in 400 males over 12 years. High wear is defined as cobalt levels in the blood above 2 mcg per liter. This is the limit where the bearing surface of the hip starts to wear excessively. The blue line shows males who have low wear and high-risk genotype, and at 12 years shows an implant failure rate of 35%. Please keep this in mind as we discuss the next slide.

These curves show survivorship of hip implants in women with respect to time post implantation. A survivorship of 1 means that there were no failures, whereas a survivorship of 0 means that 100% of the implants failed. Again, the failures shown here are due to the development of ALVAL. High wear, wear greater than 2 mcg per liter, correlates with high rates of failure due to ALVAL, no matter the genotype. However, women with high-risk genotype and moderate to low wear, shown in the dotted blue and green lines, show early high rates of failure. For instance, at 10 years post surgery, 84% of women with high-risk genes and high wear experience failure due to ALVAL. If this information were available,

this is a potential mechanism that could protect some patients from experiencing fast-acting ALVAL in the future.

According to research done in collaboration between FDA and Dr. Langton's lab, HLA genes are predictive of approximately 75% of total hip failures due to ALVAL. What you see here is a representation of the HLA genes, which produce a three-dimensional shape, which is the peptide binding group. The shape determines which antigens are more or less likely to be presented and stimulate an immune response. An example of this is in celiac disease, in which patients have genes encoding peptide binding groups which structure is particularly suited to presenting antigens derived from wheat.

In hips, evidence indicates patients genetically predisposed to ALVAL possess peptide binding groups suited to presenting peptide fragments involved in metal ion binding. The gene on the left is associated with three times greater risk of developing ALVAL than that on the right, compared to a lower-risk genotype, based on data derived from hip failures. The relative risk can be predicted by understanding the shape of the antigen binding site of this part of our genome. The same, we believe, may be true in the case of metal knees associated with pain and failure due to ALVAL.

We know that large numbers of individuals with knee implants are not content with their devices. Now that we are evaluating the explants from failed knee implants, we're noticing a great amount of wear and metal debris coming from the implants. We've also noticed significant levels of cobalt ions in the blood. And upon examining the metal tips, we've noticed that these components show a great deal of material loss. Explant wear, based on our interactions with our collaborator, Dr. Langton, pitting and metallic wear is seen across multiple knee designs. This can be seen in the optical images of the tibial trays shown at 30X magnification.

We noticed a growing number of case studies of noteworthy levels of ALVAL

associated with knee implant failure, shown here. These publications show previously unrecognized rates of ALVAL, between 7 to 20%, in failed knee implants. Both papers link the extent of ALVAL to the extent of pain, which were completely unrecognized until the cases were retrospectively reviewed. Our overarching hypothesis is that patients with unexplained painful and revised total knee replacements due to ALVAL will have a significantly greater frequency of certain genotypes.

Our goals are the following: Number one, Identify differences in HLA gene frequencies in painful or total knee replacement patients as compared to asymptomatic total knee replacements, based on ongoing clinical and revision data; number two, examine similarities in HLA gene frequency between ALVAL resulting from total hip replacements and total knee replacements to determine whether the predictive model for hips can be used similarly for knees, and number 3, to evaluate a genome for indications of genomic frequencies that will aid in biomarker research, including active peptides that indicate active metal sensitivity, sex-linked genes and genotype that indicate high risk, especially in women.

We'll have a patient population of 600 individuals, 300 males and 300 females. Seventy-five males and seventy-five females will be in each of the groups noted on this slide. Many samples, including tissue, explanted failed knee replacements and blood samples have already been collected. In order to achieve our goals, we'll contact patients whose blood and oral swab samples have yet to be collected. These will be analyzed for cobalt and chrome ion levels and genotyping. Additionally, we already have many explanted knee devices, and corresponding tissue samples, which will be analyzed for volumetric loss and ALVAL grading, respectively.

Next, we'll compare the predictive ability of HLA genes from previous work with total hip arthroplasty failure due to ALVAL with failed and painful total knee arthroplasty.

Additionally, we'll adapt the machine learning algorithm used for total hips and total knees to develop predictive modeling for metal drive replacement implanted in the knee.

HLA genes can predict approximately 75 percent of the hip failures due to ALVAL. Therefore, we'll analyze the whole genome to expand the algorithm's predictive power and continue training the machine learning algorithm to create a tool for predictive risk associated with personalized genotypic information in total knee implants. We'll consider factors such as patient clinical outcomes, patient age, sex, time to revision, explant analysis, histological samples, ion levels and full genetic information.

Our collaboratives include several institutions from the U.K., including ExplantLab, directed by Dr. Langton, and the Hospital for Special Surgery in New York City. We're increasingly getting interest from other institutions as we continue discussing this study with our colleagues, which has allowed us access to an enormous clinical dataset. This is a major strength of our study.

DR. BOWSHER: So, for final remarks, we believe this project is timely. In the future, we'll be dealing with an increasing aging population and increasing obesity rate, which is only going to put bigger demands on the orthopedic community. We believe that this is the start of a new journey. We don't have all the answers yet, but this is a step forward in identifying a patient population that will definitively enough experience delayed metal hypersensitivity and premature joint failure. Such a tool could be used to improve clinical decision making, such as choosing the implant materials to match the patient, as well as improve patient surveillance. This tool may help in other areas of medical research, especially autoimmune conditions.

Thank you very much for your time.

DR. MARINAC-DABIC: Thank you very much, Dr. Bowsher and Dr. Smith, for this outstanding presentation, which is precisely the direction where, you know, last year's

Ortho CRN had taken us, with enormous discussion on that our research should continue to focus in this area. Thank you so much.

Now, let me introduce another colleague from FDA. This time, this is a colleague from Office of Clinical Evidence and Analysis, Dr. Yeliza Torosyan, who is a physician and molecular biologist by training, currently working as a general health scientist at the Office of Clinical Evidence and Analysis. She will present the genetic evidence of sex-dependent role of particular SNPs in hip arthroplasty-related perioperative osteolysis.

DR. TOROSYAN: Good afternoon. I work at the Office of Clinical Evidence and Analysis at CDRH, FDA, and I would like to share our experience on the use of real-world data (RWD), for discovery of biomarkers as means for predictive evaluation of real-world device performance.

To position discovery of device-related biomarkers within CDRH's regulatory research efforts, I would like to refer to our 2019 Immunology Advisory Panel Meeting on Biological Responses to Metal Implants and the corresponding 150-page scientific paper. Although this paper and panel discussion were focused on metal implants, most implant safety related manifestations and mechanisms represent crosscutting issues applicable to various implantable insertable devices.

As discussed in the panel, most knowledge gaps are regarding patient rather than device characteristics. The uncertainty regarding implant safety with the related host factors presents the main knowledge gap that results in the lack of adequate pre and post-implantation testing. As a result of this gap, post panel CDRH efforts include the research of study endpoints such as biomarkers, that can allow development of new clinical and preclinical tests for more predictive assessment of real-world performance.

Our biomarker discovery research utilizes pre-existing RWD as well as unconventional data sources and analytic tools. This presentation is focused on biomarkers

for periprosthetic osteolysis (PO), which presents an adverse local tissue reaction (ALDR), driven by implant wear and corrosion debris, and potentially leading to implant loosening and failure.

In our previous study, we identified GNAS rs7121 as a candidate SNP linked to the male predominance in hip arthroplasty-related PO. In the current study, we further assess the role of GNAS SNPs, as well as GNAS-related comorbidities in development of PO. Our study was based on clinical and genetic RWD from the eMERGE, Electronics Medical Records and Genomics network affiliated with the National Human Genome Research Institute.

Data analysis and interpretation were performed using in-house, High-performance Integrated Virtual Environment (HIVE). Different in silico analytic tools and knowledge bases were used to assess the biological plausibility of GNAS SNPs as PO biomarkers, and GNAS-related comorbidities as PO modifiers.

This slide shows the details of eMERGE data transfer and processing. Procedures and outcomes of interest were identified using harmonized ICD-9, 10 codes. Among approximately 84,000 available, mostly white subjects, there were about 11,000 subjects with various arthroplasties. Due to unavailability of subjects other than white, the current study was focused on about 3,000 white subjects with hip arthroplasty, which were stratified into the male and female subgroups, with or without PO.

Despite the overall prevalence of females among subjects with hip arthroplasty, PO was more prevalent among males. A HIVE (indiscernible) clustering heatmap illustrated distinct allelic patterns of GNAS SNPs in relation to PO, including the PO male-specific cluster outlined here by a blue box. In addition, asterisks show the SNP with most distinct sex-related allelic trends. The allele of this outlier SNP had a twofold decrease among PO females, and a similar increase in PO males when compared to respective controls.

Likelihood ratio analysis further suggested the role of the outlier SNP and some other GNAS SNPs as sex-dependent PO biomarkers. Consistent with the presence of PO male but not PO female, specific SNP cluster, as shown on the previous slide, statistically significant likelihood ratios were limited to the PO males, as shown here by green shading.

Time to PO, as a time difference between the dates of diagnosis for hip arthroplasty and subsequent PO was defined in our further research. Despite the male predominance among PO subjects, females showed a shorter post-implantation time, a p-rate prior to PO diagnosis. A total of nine GNAS SNPs showed statistically significant genotype differences in relation to PO.

The main sex-dependent genotype associations were shown by the three SNPs listed on this slide. Regression analysis further suggested the combined role of sex in some GNAS SNPs in development of PO. As shown by this Venn diagram, the numbers of unique and common diagnosis in subjects with and without PO were different, thereby suggesting possible presence of distinct PO-related comorbidities in males versus females. Our subsequent comorbidity analysis was focused on the endocrine metabolic conditions which are known to be associated with GNAS, as identified by our *in silico* analysis.

This slide shows examples of our GNAS-related in silico analysis. On the left, GNAS disease outlets from the base-base correlation engine shows metabolic disorders related to calcium, glucose, and lipids, as indicated by asterisks. On the right, GNAS-related network, per ingenuity pathway analysis shows GNAS connections to biological functions and pathways relevant to glucose lipid metabolism, bone growth and endocrine regulation involving sex hormones.

Furthermore, our *in silico* analysis linked GNAS to hip prosthesis loosening. As shown in this reference study comparing RNA expression in periprosthetic membranes from infectious versus noninfectious loosening, GNAS was upregulated in the wear particle-

induced or aseptic loosening, which is a likely result of PO. Our subsequent comorbidity analysis based on the eMERGE RWD confirmed statistically significant associations with GNAS-linked comorbidities in the sex-stratified hip arthroplasty subgroups in relation to PO.

Per the odds ratios shown here, hypercholesteremia for example, was more likely in PO males versus PO females. Additional comorbidities with different likelihoods in PO males and PO females included obesity as well as calcium and other mineral-related metabolic conditions and parathyroid disorders.

The effect sex assessment also shows statistically significant sex-related differences in the likelihood of GNAS-associated conditions, such as diabetes and thyroid disorders, as shown in this PO males versus PO females comparison, by the lines and p-values in bold. The three smaller images further illustrate distinct comorbidity profiles in the sex-stratified PO versus control subgroups.

Thus, our study delivered statistically plausible PO biomarker candidates, the biological feasibility of which was confirmed by our *in silico* analysis. By illustrating the importance of sexual dimorphism, our study also underscored the guiding rule of epidemiologic evidence in biomarker discovery. Although further research is needed for developing a clinically applicable panel of PO biomarkers, our current findings helped generate hypothesis on the GNAS implications for pathogenetically-based diagnostic and therapeutic PO management.

And at last but not the least, the study continues to illustrate the role of our *in silico* evidence into this framework, which can utilize preexisting RWD, and thus can facilitate development of cost/time efficient healthcare applications. Thus, this transferrable framework can be used for the discovery of biomarkers and analysis of outcome heterogeneity, aimed to inform the use of various medical products in patient subgroups.

The use of RWD and encyclical evidentiary framework were first described in our

2016 publication in the "Precision Medicine Informatics" issue of the *Journal of American Medicine Informatics Association*, shown here, and was further referred to in our subsequent publications and presentations.

This concludes my presentation and thank you for your attention.

DR. MARINAC-DABIC: Thank you very much, Dr. Torosyan.

And now CAPT Peat and Dr. Clayton are going to led and moderate the discussion that will follow.

CAPT PEAT: Thank you so much, Dr. Dabic.

So, today we're going to have a bit of discussion related to gender disparity in the real-world research that have been conducted. I can honestly tell you that this is very exciting for us here at FDA as we focus more on health disparity as well as focus a lot more on personalized medicine when we look at the genetic makeup of an individual. So, I'll turn it over to Dr. Clayton to start with the first question, and then we'll go with the remaining questions.

DR. CLAYTON: Thank you, CAPT Peat, and this is really exciting for NIH as well, to see this attention to sex as a biological variable in gender as well as important indicators and influences of health and disease.

We had amazing speakers in this session, and maybe we could just talk generally first, kick it off with, about the fact that there are various studies that have been reported and mentioned by some of the speakers, referencing higher failure rates for various orthopedic devices in women or men. What are some of the factors that the industry, orthopedic industry and device industry needs to take into consideration broadly to help address the data that are different for different populations and different studies, going forward? What are some of the strategies and important points for the industry to consider? Any of the speakers from today want to chime in on that first?

CAPT PEAT: Well, I will just jump in really quickly because I do think that this is going to be very important as we think about personalized medicine. So, I would like to hear a bit more from Dr. Bowsher, Dr. Smith as to what are your thoughts regarding what should industry take into consideration needs from the research that you're proposing?

DR. SMITH: Sure. This is Dr. Smith. Thanks for the question. Yeah. I think, you know, some things that immediately come to mind are when we're considering enrollment in clinical studies. Like Dr. Jiang this morning talked about, we should be working to achieve equal representation, to make sure that women are included as much as possible.

DR. BOWSHER: Yeah. This is John here. I would add that, you know, we hear that women respond more aggressively to implant wear debris. So, this is more sort of longer term. I mean, we heard some presentations today with more shorter, you know, mid-term clinical experience. But maybe with long-term, these differences become wider. And, you know, that has to be disseminated through further research. But industry, you know, should be cognizant that women may be more reactive to implant wear debris, especially metals.

DR. SMITH: I'd also add to that, that, you know, as far as thinking about clinical studies though, it may also be something to consider to add in the collection of genetic information when explant retrieval is involved, make it a priority to look very carefully at blood ion level tissue analysis and material loss. Because like we mentioned -- excuse me, material loss from the explant. Like we mentioned, these are important for the context of reaction to metal.

(Simultaneous speaking.)

CAPT PEAT: I see that Art has his hand up, so therefore you have it, because I really was going to lead to Suvo, but go for it.

DR. SEDRAKYAN: No, this is a great -- many great presentations. I just wanted to

highlight that real-world evidence is really important guidance for us, about subpopulations that might still be at risk. While I appreciate the science behind doing quite a bit of genetic analysis, I think it's best if it's targeted in the subpopulations that we find still have higher risk of revisions.

Yes, 2 years might not be long enough follow-up, but I think it starts to indicate those subgroups. I really think it would be helpful if we can better understand that age effect, younger females, whether the risk is related to any implant factors or is it related to genetic factors, for example, anything that we can understand well there.

In males, Suvu's presentation is important because it indicates the infection-related septic sort of revision, early 2-year period is the main factor. So, I think, what are the implants out there that might reduce this infection, and whether we can evaluate them now, and if they're on the market now. If manufacturers are producing those products now, we'd like to see if there is a way to evaluate them in the real world and understand their performance.

We work with CAPT Peat and the FDA team to come up with objective performance criteria that include septic revision occurrence within 2-year period. So, I think we have a lot of tools within Ortho CRN to help manufacturers to do studies in this space.

CAPT PEAT: Yeah. I couldn't agree with you more. We're seeing a lot of failures with the hip and knee devices, so I think it's going to be very important for us to have broader discussions.

So, going back to the presentation by Dr. Jiang, she really gave the starting point to us having discussions on sex and gender, and racial disparities.

So, Dr. Jiang, in reviewing the information that has been provided in our various submissions to FDA, what are some of the things that you are thinking about can be, shape the future look of devices when we look at it from an academic community or clinical

community, and how can we broaden more inclusion of a diverse population in clinical studies?

DR. JIANG: Thank you, CAPT Peat. That is a very good question. From my experience, from looking at the data, the clinical trials we have reviewed at FDA here, we have a quite mixture of different, you know, types of studies and enrollments.

So, one thing that struck me is that because different diseases, they have different, you know, distributions in different subgroups, so I think, you know, to say an even distribution between different subgroups may not be realistic or necessary. So, it's more a reflection of the real disease distribution, I think is the most important thing that what, you know, investigators should keep in mind when they design a study, and how to recruit, you know, appropriate representation for different subgroups, so that we can have good data to work with later on, in our analysis.

CAPT PEAT: (Indiscernible).

DR. JIANG: Sorry, CAPT Peat, I couldn't hear you very clearly. How about everyone else, like Janine?

DR. CLAYTON: Yeah. CAPT Peat, your audio was garbled. Can you try again?

CAPT PEAT: Yeah Janine, can you hear me now?

DR. CLAYTON: No, yeah. You're still garbled. Let --

DR. SEDRAKYAN: It might be your WiFi.

DR. CLAYTON: Okay. Let me go ahead and ask a question, and we'll see if you come back.

So, one of the questions I had was about potential confounders, and this is for any of the speakers. You talked, we talked about sex, gender, even race and ethnicity can sometimes play a role in outcomes. What are some potential other factors that could be confounding, you know, theoretically, stage of disease, likelihood of being referred early,

different patterns of disease by sex? And so maybe one of the other speakers who hasn't talked already could comment on potential other confounders, especially for our audience.

DR. TOROSYAN: I would like to chime in. This is Yeliza Torosyan from the Office of Clinical Evidence and Analysis. I would like to bring to your attention that although our presentations today were mostly focused on the role of sex, there is also a role of race/ethnicity as an additional demographic factor, so that presents an additional layer of complexity, if you will.

So, as an example, some adverse outcomes, the safety profile, say in black females may be different not only from black males but also from white females or Hispanic and other females, as we see in our preliminary results. And we need to face that complexity. And when we are talking about the environmental factors and the demographic trends in particular, we also need to remember that some of the genetic factors, let's say, can negate the consequences of the -- negative consequences of some socioeconomic factors, or they can potentiate them.

And we need to face that complexity and take the epidemiologic and genetic evidence in their entirety when we are trying to come up with the right solutions to improve the real-world evidence and the real-word performance in patients and populations and really inform the use of the different devices in patient subpopulations. That's the only way of improving real-world evidence, and predicting, in the pre-implantation period, to predict the post-implantation performance in different patient subgroups.

And I also would like to add a minor comment. Although we talked about metal sensitivity in some of our implantations, and that is true that metal sensitivity can accelerate device failure in certain cases due to development of ALVAL, as Drs. Bowsher and Smith were talking about, but as was voiced in the discussion during that panel that I

mentioned in my presentation, metal sensitivity is actually one of the -- it might be one of the major issues, but it's not the only issue. And there are crosscutting mechanisms of biological reactivity that are applicable to other components, non-metal components in devices.

And again, we need to face the complexity due to device-related factors and due to patient-related factors. Thank you.

DR. Bowsher: And this is John here. It's very likely that women may be more reactive to polyethylene wear particles compared to males. So, you know, like Dr. Torosyan was talking about, this is not just simply a metal sensitivity, although we're, you know, we're homing in on metal sensitivity because we've learned all this great information from the failures of metal on metal, which was a unique opportunity where we had this, you know, clinical datasets where we could find all the information of the genes and the outcomes and metal ions and the wear and put it all together. So, you know, there's other factors involved as well, so.

CAPT PEAT: (Indiscernible).

(Simultaneous speaking.)

DR. JIANG: Maybe I could repeat the question, or maybe Dr. Clayton?

DR. CLAYTON: Sure. I think --

DR. JIANG: Go ahead. Yes.

DR. CLAYTON: I think it was for -- Suvu, I think this question is for you, and I think it's related to what conclusions might be drawn, related, you know, solely to age and gender. Are there other factors, you know, beyond sex and gender that need to be considered from the presentation that you gave? And also, any questions -- I think Dr. Peat -- CAPT Peat was also looking more towards the age effect. Can you comment on that?

MS. ARYAL: Yes. We -- like you saw in our results, we found that younger patients

were at higher risk than older patients, and notably younger males, right. We saw that males were the higher risk for revision, all-cause revision and septic revision. But when we look at the subgroup, younger patients who were younger than 55 had the highest impact. And I think there's some prior evidence that older patients were at lower risk, but we definitely need to look further into just the subgroups and a targeted analysis on looking at just the male population in these different subgroups. I think that would be something to look in the future.

DR. CLAYTON: Thank you very much. You also commented in your presentation about surgical site infection rates being higher among men. I believe it was your presentation. And so, we know there is sex differences in the immune system, and Danica mentioned this in the outset, or other -- somebody else mentioned, you know, even that playing out in the COVID pandemic that we're seeing.

Does anybody want to comment on the importance of including basic differences in immunology in any of this? Because you've highlighted it very nicely. In fact, at NIH, we're even going back and looking at our sepsis models, to see if those models are true for both males and females. Any of the speakers want to comment on the importance of that?

Dr. Torosyan, maybe?

DR. TOROSYAN: Yes. I actually was going to talk for a minute. I would like to refer to another ongoing project that is part of our post-panel research efforts. We call it the True Scope Projects. And it utilizes preexisting clinical data, but one of the farther goals is trying to identify the comorbidities that can be based on some immune mechanisms, and trying to deduce what are those immunological, immunity-related mechanisms, which would involve not only that community as well, for example, but also (indiscernible) community and the extended foreign body response, and the role of chronic inflammation.

That's the part that I am interested, particularly. This gives me a chance to say that I

actually worked in the autoinflammation as well, at NIH. And so the role of inflammation is the latest addition to our current understanding of implant reactivity. And we will try to deduce these common immunological mechanisms based on this preexisting clinical data. And that is a really large-scale effort that involves tens of thousands of patients. Thank you.

DR. CLAYTON: Thank you very much.

CAPT PEAT: Thank you so much. Oh, sorry.

DR. CLAYTON: Oh, CAPT Peat, you're sounding great. Go ahead.

CAPT PEAT: Yeah, thank you.

DR. CLAYTON: Dr. Jiang has her hand up.

CAPT PEAT: Yeah, I saw her.

Dr. Jiang, go ahead and close us out, because we're at the tail end of this particular break, as fascinating as the conversation is.

DR. JIANG: I just want to have a quick comment. I think, CAPT Peat, your -- when you asked question, and Dr. Clayton, you mentioned about other factors. So racial and ethnicities are other important factors we should consider, definitely, as well but I don't think we have mentioned that yet. So I just want to add that on. Thank you.

CAPT PEAT: Yeah, and I was thinking also some other confounding factors could be accessed. Because I know, with Suvo's research, which was quite timely, typically you are able to get data from Medicare for greater than 65, but her research really showed under that particular age group.

Do you think the findings that you had, Suvo, was expected or unexpected? Because I thought it was just remarkable, what you found.

MS. ARYAL: I think it is remarkable, but we -- some research, prior research shows that younger patient -- again, I said this already, have a lower risk. But because we were looking at males versus females, I think this is pretty novel to find that, you know, younger

than 55 are at the highest risk, and particularly males. So, I think that information is novel.

DR. BOWSHER: This is John here. Doesn't your immune system generally weaken as you get older? I know also you can, you know, influence your immune system by your diet, and eating better but I mean, I think we believe in general that these factors will be small when looking at our data. But in terms of age, I would envision immune system getting worse.

DR. CLAYTON: I don't know if others want to comment, and we're close our time.

Danica?

CAPT PEAT: Yeah, I think they want to close the --

DR. MARINAC-DABIC: No, I just want to say, I was just going to say that this question really leads to important notion that we all try to sort of underscore here, that importance of convergence of epidemiologic traditional methods with the genetic data and looking at the outcome research together, to help guide the actual analysis that can be done at the basic science level. So, your -- actually is, speaks about, you know, to the fact that we would need to help guide this type of next level studies, by better cooperations in this space.

CAPT PEAT: I know that we're at time, and -- but it does show that we need to do more research, right. This is not the end of the story. It's the beginning of the story. You can see for the past 12 months we have been doing quite a bit of things. And so, there is more questions that we need to answer, so I look forward to seeing the results next time we have our next Ortho CRN, to hear more about the results and what are the next future research we should be thinking about for our patients, both nationally as well as internationally.

So, thank you all, to all of our presenters, as well as to my co-moderator. We'll see you at the next group discussion for the next cohort of individuals before we go to the

break.

So, Dr. Dabic, put us on break.

DR. MARINAC-DABIC: Yes. So, now we will have 10 minutes break, and we'll reconvene with a new set of fantastic speakers and moderators. Thank you very much for a fantastic discussion, and great contribution that you made to today's meeting. Thank you.

(Off the record at 10:24 a.m.)

(On the record at 10:33 a.m.)

DR. MARINAC-DABIC: Just a reminder, we are still in the first session of our conference today. This is the second section of that session. We have three distinguished speakers. First, we are going to hear from Paul Voorhorst, the head of the Clinical Science and External Research at DePuy Orthopedics. He's going to talk about industry perspective on using real-world evidence for regulatory decision making in orthopedics.

MR. VOORHORST: Hello. This is Paul Voorhorst. I'm the Vice President of Clinical and External Research for DePuy Synthes, a Johnson & Johnson company. I would first like to just thank the organizers for this opportunity to speak on the topic of real-world evidence for regulatory decision making in orthopedics, from an industry perspective. These are my disclosures.

I would like to briefly cover three topics today: Objective performance criteria, or OPC study designs; post-approval studies, or 522 studies, and also indications expansions. Let's first look at objection performance criteria or OPC designs.

As a way of background, let's talk about primary total hip and knee replacement. These are mature, well-established and successful surgical procedures that are performed in very high volumes, globally. There are numerous high-quality national joint registries both in the U.S. and outside the U.S., with decades of data available to researchers in aiding in the establishment of OPC for our pivotal premarket investigations. Adoption of

premarket OPC designs could improve timely access to innovative devices.

As I mentioned, there's multiple registries that could be used for establishing OPC criteria. Within the U.S. there is high quality registries in joint replacement that are run by Kaiser Permanente, of course TJR, Hospital for Special Surgery, MARCQI, or the Michigan Registry, and also the American Joint Replacement Registry. Outside the U.S., there's multiple national joint registries that have been in existence for decades, with very high-quality data as well.

I'd like to focus just briefly on data linkages. The American Joint Replacement Registry has recently linked their registry data to the data from CMS, which provides a very high-quality data source for joint replacement. In addition to that, there are local data sources, for example, in New York State, the Statewide Planning and Research Cooperative System or SPARC System could also be used for the data linkages.

Now let's change focus and take a look at post-approval and 522 studies. It's important to understand how these studies are conducted by industry, and it really depends on the research question, and the best data source to address that question. New device with no registry or available real-world evidence oftentimes uses IVP rollover patients for a new study, a post-approval study.

When registry data are available, which is common for implantable devices such as hip and knee replacement, they provide a rich source of data for those post-approval studies as well. In terms of post-approval studies for label extension, with extensive use of the intended indication available in electronic health records or hospital databases, this can also be an excellent source of real-world evidence.

Let's first look at some difficulties that industry has with complying with post-approval studies or 522 studies. There oftentimes are difficulties in an enrollment. This can happen for multiple reasons, one of which is difficulties in enrollment. On the total hip side

of things, the move towards larger femoral head sizes made it very difficult to enroll patients into smaller diameter femoral head size studies. Thereare also difficulties in patient retention. Long-term follow-up is difficult, and 5 and 10-year follow-ups are burdensome to the patients that have no symptoms, and no problems.

Patients move away in this patient population, to warmer climates as well. And for that reason, it's easier to achieve 5 and 10-year follow-up in national or U.S. registries that have that national cradle-to-grave follow-up system. In addition to barriers to using OUS national registries is the desire that the sponsors demonstrate matching of patient regression and disease progression between OUS registry populations and U.S. populations. In addition, barriers to using electronic health records can sometimes occur, while demonstrating reliability and relevance of real-world data.

Having said this, there are examples where industry has successfully used real-world evidence in support of post-approval studies. In the recently published examples from the FDA in 2021, the CoC, ceramic-on-ceramic system did use real-world evidence in support of their post-approval study.

Let's take a quick look at an example in that ceramic-on-ceramic total hip system, the first PMA approval in 2010. That approval came along with multiple post-approval study commitments for the 28 mm and also for the 36 mm head size. These were all prospective studies, with the exception of PAS Number 3, which also included a data population from real-world evidence sources in the National Joint Registry in England and Wales, and also from the Australian National Joint Registry.

Let's briefly look at what improvements might be possible. For post-approval studies, they're designed with good scientific principles when the product's approved, but it doesn't always account for feasibility of implementing that study. Preferences for data on each device configuration, for example, in length of follow-up can be problematic. Greater

flexibility to adapt and utilize other data sources, reflecting reality of what's happening in the real world, would be helpful. And more flexibility in accepting OUS national registry data for long-term follow-up, that cradle-to-grave patient follow-up in OUS countries can give a much better follow-up by data linkages and national healthcare systems. The FDA desire to demonstrate comparability of populations between OUS and U.S. populations could be relaxed.

Can real-world evidence become the sole source of evidence rather than adjunctive? I'd like to think so. Registries have a much larger, and more representation of general use patterns, with diverse levels of surgeon experience. More importantly, inclusion of operational minority subgroups would be easier to be met through real-world evidence data sources. Greater use of real-world evidence from healthcare care systems, electronic health record databases or data are fit for purpose, and a risk-based assessment of real-world evidence reliability and relevance can focus on issues that matter when comparing two groups in the same real-world evidence data source.

And now let's take a quick look at just a couple of ideas around indications expansion. How could real-world evidence support new indications? A couple of ideas and thoughts. Use of technology that's on-label outside the U.S. to support new indications in the U.S., for example, antibiotic-coated devices and antibiotic bone cement. These are both technologies that have been approved outside the U.S. for a long time and have associated with them a whole lot of real-world evidence. Another example might be hip replacement device configurations, for example, addition of femoral stems or surgical techniques that have been approved outside the U.S. Could that data be used to expand indications in the U.S.? I think maybe so.

And also, what's the role of Ortho CRN in this research? I'd like to think there is a role. There's a lot of data sources in national joint registries that are part of the Ortho CRN

network. It could provide a very rich dataset for new indications.

To briefly summarize, how can industry and the FDA work together to do better in these programs? First, flexibility to consider OPC study designs in a premarket setting. Secondly, feasibility in studies, and adaptability of study designs and milestones based on market usage. And also, flexibility, in accepting real-world evidence, more pilots for using real-world evidence from healthcare systems' electronic health record databases for post-approval and 522 requirements, and an expansion of indications.

Thank you again for the opportunity to speak and thank you for your attention.

DR. MARINAC-DABIC: Thank you, Mr. Voorhorst, for a very informative presentation, and also thank you for very practical and clear recommendations for the IDA and the CRN community.

Now the next speaker is Dr. Brent Showalter, who is the Assistant Director of the Division of Spinal Devices at CDRH's Office of Orthopedic Devices, and he will be giving a presentation on evaluation of real-world evidence, adverse events and the risk factors in patients undergoing spinal fusion with interbody fusion devices.

DR. SHOWALTER: Hey, good morning, everyone. Thank you very much for that introduction. If we can move to the next slide, please.

So, I'd like to start with a little bit of background information that many of you are already familiar with. So intervertebral body fusion devices, also known as interbody fusion devices or cages, are devices that are inserted in the disc space between two adjacent vertebral bodies with the intent to facilitate fusion. Some can be used individually, while others, as shown in the figure, are used in conjunction with other devices, such as pedicle screws.

When intended to be used for intervertebral fusion, most of these devices, as identified under 21 C.F.R. 888.3080 are regulated using premarket notifications, otherwise

known as the 510(k) pathway. Under the 510(k) paradigm, we clear, not approve devices that are found substantially equivalent to a legally marketed predicate device, in other words, one that has already been cleared on the market.

Nonclinical testing for these devices has been developed and is usually adequate to make a determination of substantial equivalence. However, we should recognize that nontraditional designs or new indications for use may require clinical data to support marketing. Next slide, please.

When evaluating clinical data, or literature supplied in support of intervertebral body fusion devices, some important elements that we consider include, but are not limited to first, the indications for use. For these devices, the indications generally include the treatment of degenerative conditions, but may also include other conditions, such as spinal deformity.

The second example is that the type of film material used within an intervertebral body fusion may lead to different performance outcomes, as well as dictate a different regulatory pathway. For example, per the regulation, a PMA rather than a 510(k) would be required for cages using graft with bone morphogenic proteins. Next slide, please.

While fusion procedures with intervertebral body fusion devices have a high success rate, there are also associated risks and potential adverse events. This slide does not contain a complete list of the potential adverse events, but rather it highlights a few common examples. So, all cages are subject to adverse events such as pseudoarthrosis, device migration, and fracture.

The devices themselves come in a wide variety of configurations to accommodate different patient anatomy, spinal levels and surgical approaches. To see some of these differences, on the top right is a PEEK monoblock cage. In the middle is an additively manufactured cage, and at the bottom is a cage with screws for integrated protection.

Some adverse events are either unique to or have incident of -- have a higher incidence because of a technological feature. For example, about 75% of reported MDRs for additively manufactured cages are for fracture during implantation. In comparison, failure on implantation for standard PEEK or titanium cages is relatively rare. Integrated fixation, such as screws or other types of anchors, add another component type that can fracture. And fracture of these anchors, or the anchor-implant interface can be more common than that of the device bodies themselves. The anchors can also lead to vertebral body damage, either during implantation or over time.

Although these and other adverse events have been regularly reported, we don't have definitive data on how often these events occur, or how significantly they impact the overall clinical outcomes. For this reason, we're very interested in using registries to assess the clinical impact of these adverse events. Next slide, please.

The NEST test case related to the -- there is a NEST test case related to intervertebral body fusion devices. And this particular test case was supported by Lahey, PEDSnet and Johnson & Johnson. It represents the first venture in the spinal device product sector under this program, and it should be lauded for its thoughtfulness and vigorous methodology. So, the agency interacted with the Lahey and Johnson & Johnson team at several points during the study over the last couple of years, and their openness to feedback is evident in the phase II study, which is attempting to address the needs for additional endpoints such as radiographic data.

Specifically, one of the elements in the phase II study is to compare information available in electronic health records with findings from independent radiographic assessments of the original radiographs. This study was designed, or rather is intended to evaluate whether real-world evidence could enhance device postmarket surveillance, and also to demonstrate that there was no outstanding safety or effectiveness question related

to the devices in this test case.

While the generation of real-world evidence holds multiple applications where data collected is reliable and relevant, in this case, the results may serve to validate the safety and effectiveness of the devices under study, as well as lead to labeling changes, serve as surrogate data for other marketing applications or device refinements down the road. Next slide, please.

In addition to this NEST test case, we have initiated two safety studies intended to evaluate the adverse events related to certain common technological features of interbody devices. These studies are collaborations with my office, the Office of Orthopedics, the Office of Clinical Evaluation and Analysis, OCEA, within CDRH, and external contractors. All of these groups and many contributors have been very helpful. They've provided valuable insight in formulating these studies, for which we're very grateful.

The data sources that we're drawing from include registries and electronic health records. Both of these studies compare different types of cages. The first is a comparison in clinical outcomes between additively manufactured devices and traditionally manufactured PEEK or titanium implants. The second is to compare integrated fixation cages that are used without any supplemental fixation to non-integrated fixation cages. Although there are nominally two different studies and comparisons being made, the majority of the current study designs for those two studies are the same. Both focus on procedures performed in the cervical spine, with the initial procedure occurring between 2016 and 2018. This time frame will allow for up to 2 years of follow-up past the initial surgery. Next slide, please.

In these studies, we will be seeking a wide range of patient demographic, and surgery-specific information, including but not limited to age, gender, smoker status, payer, primary diagnosis, surgical procedure and current activity levels, and any comorbidities

these subjects may have. As I noted earlier, there are several adverse events that are related to these surgeries. To simplify these initial safety studies, we are currently focusing on patients that undergo revision, or secondary surgery.

For those patients that are identified as having a secondary surgery, we will look further at the records to determine the cause of reoperation, if possible. These causes may include adverse events such as fixation or device failure, a lack of fusion, device migration, pseudoarthrosis and vertebral body damage.

We anticipate the completion of these studies will give a much better understanding of the frequency and the severity of the adverse events related to intervertebral body fusion devices. The lessons learned on these initial pilot safety studies will also be used to guide future studies, such as a look at a broader range of adverse events, and devices used in the lumbar spine. We hope to glean data from these safety studies that will better inform our premarket and postmarket, and in addition, we hope to take lessons learned from this research study to make future research projects more efficient. Next slide, please.

Thank you very much. Thanks for listening in, and that concludes my presentation.

DR. MARINAC-DABIC: Thank you very much, Dr. Showalter. This was fantastic presentation, and I look forward to hearing more about the successes of your program.

The last but not the least speaker in this session is Dr. Liz Paxton, who is the Director of Kaiser Permanente National Implant Registry Program. She is a national and international leader in registry science and was inaugural co-chair of the Orthopedic CRN and International Consortium of Orthopedic Registry effort, leading also International Society of Arthroplasty Registries.

DR. PAXTON: Thank you, Danica. Are my slides up? There we go. Thank you very much. And thank you for the opportunity to present our experience with the Kaiser

Permanente registry, using evidence-based medicine to drive quality improvement efforts. Next slide.

I'll first start off by providing a brief background on the slide, our spine registry, and then share some specific examples with you on how we use the registry for quality improvement and research purposes. Next slide.

The registries were developed in 2001, and our registries were specifically designed to evaluate outcomes associated with devices, to identify patients at risk for poor outcomes and to identify clinical best practices for quality improvement, as well as identify best performing devices for our patients, and to allow us to conduct comparative effective research. Next slide.

Our registry leverages our electronic health record, which is Epic, in which we can capture information on patients, the implants, and have developed comprehensive electronic screening algorithms to identify outcomes that are then followed by chart review, to confirm. The cornerstone of our registries is a SmartForm, and that's displayed in the next slide. Our SmartForms are prospective data collection, completed by the surgeons, and integrated in the surgeon's workflow, that allow us to capture important clinical information such as diagnosis, approach and symptoms, as well as level of the spine. Next slide.

This allows us to capture patient procedure implant and outcomes for our patients for our comprehensive database for implant surveillance. Next slide.

Next, I'll briefly share some examples of how we use our registry for quality improvement. Next slide.

We currently have over 70,000 spine procedures documented within our registry and have information on the spinal region as well as patient characteristics associated with those particular implants. Next slide.

Most importantly, we have outcomes that are validated through chart review, and allow us to look at variation by surgeon, medical center and region. And that includes ED visits, readmissions, mortality, reoperations and operative nonunion. Next slide.

This is an example of one of our quality initiatives in which we use the registry to look at lumbar spine decompression. Next slide.

We specifically were evaluating the impact of reduction of length of stay and determining if other quality metrics were affected by that reduction. And as you can see, we demonstrated there was a reduction in length of stay, and neuro and ortho, while maintaining those quality metrics. Next slide.

Next, I'll provide a couple of examples of how we used our registry for research purposes. Next slide.

We have over 13 publications in peer-reviewed journals since 2014. Next slide.

This first study evaluated operative nonunion rates in posterior lateral lumbar fusion with pedicle screws and anterior lumbar interbody fusions with pedicle screws. Although PLF plus pedicle screws accrued operative nonunion rates were slightly higher, when we adjusted for patient and surgical covariates in a multivariable analysis, we did not observe a difference between a PLF plus pedicle screws versus ALIF and pedicle screws. We also did not observe a difference in one versus two-level fusions, or fusion level. Next slide.

This other recent study evaluated reoperation rates for adjacent segment disease in posterior cervical fusions, and specifically compared stopping at C7 versus T1 and T2. Creep incidence rates were similar in stopping at C7 or T1 and T2, as well as results with a multivariable analysis. Next slide.

This final study that we'll share with you compared titanium rods versus PEEK rods, and determined if there was an association with a lower operative adjacent segment disease risk. And in a propensity score matched analysis, using Cox regression, we did not

observe a difference between the two. Next slide.

So those are some of the examples of the ways that we use our registry, both for quality and research purposes. Thank you.

DR. MARINAC-DABIC: I would now like to invite our moderators to lead a discussion on this very important topic for the Orthopedic CRN.

CAPT PEAT: Thank you so much. Thank you to all of our presenters. So, the first question that I had goes to Dr. Showalter.

I see you with your big smile. So, thinking a little bit about the research that you're conducting, what are some of the specific adverse events related to intervertebral body fusion devices of greatest concern to our reviewers? Are there similarities, or different concerns for cervical versus lumbar intervertebral body fusion devices? So that's a two-part question.

DR. SHOWALTER: Yes. So there -- I mean, the devices are very different, between cervical and lumbar, because of the different loads and things placed on them, right. So, one of the reasons why we focused on cervical is actually there is -- that procedure is very well established, and there is relatively little variation in the cervical disc space, whereas with the lumbar, with the lumbar devices, there are a lot of different cervical approaches. So, there is an anterior approach, transforaminal, posterior, right. So, there's a lot more variation in the types of devices that are in the lumbar space. So, we thought for an initial study that we would focus on the more established, the cervicals. We had fewer options to choose from.

In terms of adverse events and things that we worried about, you know, I think the ones that I highlighted in my presentation are some of the bigger ones, right, so implantation -- sorry, fracture during implantations of additively manufactured. Also related to that is kind of the dynamic performance over time of additively manufactured

devices. With integrated fixation, there are lots of adverse events, so screw loosening, or toggling of the screw and different damage to the vertebral body.

And I think what we're trying to get a better handle on is how often these are actually occurring during real-world use. And we want to use kind of the frequency and severity of these to guide how we review these devices in doing clearances.

CAPT PEAT: Very well said.

We'll turn it over to Art, because I can see his hands are up again.

DR. SEDRAKYAN: I'm going to -- well, all right. Sorry, but I thought I could just raise hand.

But I think congratulations, Brent, this is really fantastic, important to embrace real-world evidence and ability for us to leverage data in orthopedics, from charts, from right, like a Kaiser registry and many other sort of -- sometimes claims data can be also made to be important contribution now that we have ICD-10 and wonderful opportunities. I really think like this, the amount of data out there that is accumulating, the number of devices gives us this chance to do more work.

Can you comment about your interest in like a spine network development? And the reason I'm saying, because Liz Paxton, who leads the Kaiser registries just presented this wonderful chance of more than 10 million people in a country, in a closed-circuit system, captured in terms of follow-up, which is really unique for us. I mean, our health systems are limited, because once people get operations in, let's say Weill Cornell or New York Presbyterian Hospital or Columbia, they can go get subsequent care anywhere else.

Well, when you -- sort of in Kaiser, they stay in, and there's only like 10% attrition rate over the very long period of time. So, what -- can you comment about that?

DR. SHOWALTER: Sorry, was that question for me?

DR. SEDRAKYAN: Yeah. I was just --

DR. SHOWALTER: Yeah? Okay, good.

DR. SEDRAKYAN: -- thinking about that network development --

DR. SHOWALTER: Yeah. Yeah, no, I completely agree with you. I think that's something that the patient follow-up is something that is very much of interest for us, right. And as you mentioned, you know, having a single system like Kaiser be able to track patients is a huge boon, you know, as something that we've run across in the studies that we have now, right.

One of our primary objectives is tracking secondary surgery, but we have to acknowledge that in several of the registries and data sources that we've looked at, knowing that some of the patients that got the initial surgery are not going to be tracked by the registry, so we don't know -- you know, we are going to be using some of those secondary surgeries, and it's a little bit difficult to account for that.

With some of the data sources, we're trying to use Medicare and Medicaid data to help track it a little bit better. But as you mentioned, you know, a single spine registry, you know, a system like Kaiser has set up is very advantageous for that reason.

CAPT PEAT: Yeah. I mean, Kaiser is an excellent system, and I know that Dr. Paxton was able to gather a lot of information that's helpful to the community, utilizing the data that's collected in their registries. Though we are also, for this research, utilizing other areas as well. So, we're going to not just look at Kaiser, but equally we're looking at registries such as in ASR and other areas, so that we can look at the full gamut of the information related to our patients and being able to address the research questions, and also to see if it elucidates other questions that we haven't considered, as we are reviewing our products. So that -- I just wanted to make sure that we note that this is going to be an expanded study as we go along.

Dr. Paxton?

DR. PAXTON: Hi. I just wanted to mention that there are so many benefits in terms of collaboration, nationally and internationally. Even for a system like Kaiser Permanente, where we have very low attrition rates, in particular within our system, we have national contracts that determine the manufacturers and the implants that we use. And so, all of our results are related to those implants and those contracts. So, we appreciate the opportunity to collaborate with other groups and systems to determine outcomes associated with other implants that we may not have on contract and can't currently evaluate.

CAPT PEAT: Absolutely.

Dr. Clayton?

DR. CLAYTON: Dr. Paxton, can you comment on how the registry data that you've collected for patients with spinal conditions have affected the clinical practice in the context of Kaiser? Just give us a little bit more of how that has affected clinical care.

DR. PAXTON: Yeah, I can. One of the best probably examples we have is that we've looked at the impact of BMP in a spinal surgery and did not observe a difference. And this was several years back, and provided that information to the physicians, who then decreased in their usage of BMP, which is a costly addition to the surgery. That's one example.

Other examples are, providing feedback on outcomes at specific centers. And that has identified centers with higher rates of reoperations. And we were able to provide that information and see changes as a result of looking at that more in depth. In addition, we provide a surgeon-specific report, so -- in a confidential manner. And so, the physicians know how their patients are doing in relationship to those of their center and regionally as well as nationally.

DR. CLAYTON: Okay.

CAPT PEAT: Yeah, I think that's very interesting, Dr. Paxton. And I know that you presented on some of this information at previous Ortho CRN. So, we know that collaboration is essential, not just for those of us who are regulators, but also within academia as well as other federal governments and researchers.

Going back to Mr. Voorhorst's presentations, I thought it was really good. There was a slide that really focused on things that FDA can address, such as really focus in on feasibility studies, accepting real-world evidence, as well as OPCs. And I do know that it's not just isolated to the FDA doing these things, but it's also collaboration. So I know we've been working very closely in the Ortho CRN community on developing OPCs for hip and knee arthroplasty devices. So, we anticipate that will be published soon.

But you also mentioned an aspect of more pilots using real-world evidence. Could you expound on that, and how fast can industry and other stakeholders support that particular posture?

MR. VOORHORST: Yeah, I think -- so first of all, thank you for the question. A couple of things come to mind, right. And, you know, these are, these as you point are collaborations. And so, the topics that come to my mind, listed at the end of the presentation, around antibiotic-coated devices, for example, or antibiotic bone cements. Those are examples, right, of technologies that have been on the market for many, many years in Europe, and the outcomes of those are captured.

We have the luxury, in the joint replacement space, of having some of the longest running, high-quality registries in the world. And so those registries could be a rich source of data to explore whether or not there is sufficient evidence to have a discussion around raw need indications for antibiotic bone cements, which right now in the U.S. have very limited indications for use.

CAPT PEAT: Go ahead, Dr. Clayton.

DR. CLAYTON: Did you want to follow up on that, CAPT Peat?

CAPT PEAT: Yeah. I was just thinking that I -- you know, I hear your feedback and I think you bring forth some really interesting considerations when we're looking at it from a global perspective. I think my question really stems from having a little bit more granularity on the use of that last bulleted point where you spoke of more pilots to use in real-world evidence. I don't think I was clear on the response for that.

MR. VOORHORST: Okay. So, I -- when I heard pilot, I think of, you know, identifying projects, right, that could be, serve the purpose of learning, around what the strengths and the limitations are, of the real-world evidence that's available for different specific devices. And so, when I think of a pilot, I think of looking at, for example, a very specific device, if you would, and identifying sources of that real-world data, that could then be in collaboration with multiple stakeholders, looked at as a project to understand, and learn about the strengths and limitations for that specific pilot. Does that help?

CAPT PEAT: Yes. Much clearer, thank you.

MR. VOORHORST: Thank you.

CAPT PEAT: Dr. Clayton?

DR. CLAYTON: Kind of a different area, I'd like to just bring to the speaker's attention an issue that I'm sure you're well aware of, which is the relative dearth of sex disaggregated data being reported in scientific journals. And this meeting is such a fantastic one where we're focused on these issues, and I've been really impressed by the quality of the data analyses that have been presented. And that's a challenge in academia, and just in terms of the data being published.

In fact, about six years ago, a review on high-impact orthopedic journals found that less than 1/3 of those studies, you know, disaggregated their data by sex for the primary outcome. Can any of the speakers comment on strategies for improving that, and whether

you believe that's changed over the last 6 years? I mean, from NIH, we put out our sex as a biological variable almost 6 years ago, so I'd really be interested in your thoughts on ways to improve, because all of you are very interested in these issues.

MR. VOORHORST: So, I'll kick off, with just from an industry perspective. You know, I think, in -- when we're running, for example, company-sponsored clinical studies, those from a publication standpoint, certainly we would split out results by gender. But what we've observed is that I think there's a need for further education with the journals and the reviewers around real-world evidence. I don't think that there's a broad understanding of registry science, and I think in that regard it would be helpful to go through, on an educational campaign, if you would, to up the understanding and knowledge around registries.

And I think those -- you know, those -- and the reason I bring that up, I guess is that, you know, I look at the registries as having a very, very rich, you know, a rich dataset for exploring gender and racial diversity and outcomes, much broader than a clinical study would have.

DR. MARINAC-DABIC: If I could (indiscernible) and step out a little of OCEA to say a couple of things about where we've seen some gaps in strategically coordinated registry efforts generally speaking, you know, sex variable always is collected, always there are all sorts of ways of how things can be improved in terms of harmonization of the data elements. Gender is not collected. We are always pushing toward that. There have been a lot of efforts across different clinical areas so to actually harmonize the way of how core minimum datasets are collected, which I think is going to be the greatest contribution of that, of the larger CRN community of -- a lot in community that we establish.

Then maybe that's another thing that potentially, with NIH, we can maybe explore some ways of figuring out where additional gaps are, that we can, as agencies work

together. But those are really important points. One thing is about a curation of the data and, you know, analytical novelties and all that, but just the basic collection of the data. This is still a lot of efforts that need to be actually inserted there for us to actually have that evidence.

CAPT PEAT: Yeah, I couldn't agree with you more, Danica, because I do think that is going to be important for us to have that broader collaboration, particularly since we have Dr. Clayton on the line here, with NIH. I think that would -- when I thought of Paul's slide, when he talked about pilot, I was thinking more about some additional research that we could collaborate with NIH and other entities to be able to really just have some common data, weeds data elements within these various registries.

And compared to some of the other device-specific areas, when we look at real-world evidence and the associated data, they're a little bit narrower and still best of the number of registries and linkages and so forth that they have, compared to the orthopedic field. It's just, you know, there's so many different ways that you can capture the data, but how do you collate the data to actually focus on patient outcomes, and what are the concerns that we're seeing, whether it has to do with revisions, or pain, or sex and gender and so forth?

It's just, you know, there's no commonality. There's no uniformity. So, I do think that is where I was thinking when you mentioned a pilot of real-world evidence and how we can work together as a community to be able to address that.

MR. VOORHORST: Well, it's an excellent point.

DR. CLAYTON: And thank you, Danica and then CAPT Peat as well, just for those comments. I think there are real opportunities for harmonizing how we collect sex and gender, very challenging, but I think we've made a lot of progress, perhaps on different parallel fronts for different reasons and different contexts. But I do think it's a good time

for us to come together to be able to share that information. In fact, just this week, NIH put out a new funding opportunity announcement around COVID in pregnancy, and we're collecting some common data elements there, just within the female sex. So, it's not just sex differences, it's even reproductive health and how we collect that information and having that harmonized.

So, Dr. Marinac-Dabic, I'm going to send it back to you.

DR. MARINAC-DABIC: Yes.

DR. CLAYTON: Thank all of our speakers for this session, and my co-moderator for just a great discussion. Back to you, Danica.

DR. MARINAC-DABIC: Thank you, so much. It was fabulous session, absolutely. And thank you to our fearless leaders from NIH and FDA for making this really great success, also to all of our speakers and contributors to this session and all the planning team. I'm also very proud that we are really on time, so we actually can have a full hour for lunch, 60 minutes. So, we will see you back at 12:15.

(Whereupon, at 11:19 a.m., a lunch recess was taken.)

1

2

3

AFTERNOON SESSION

(12:15 p.m.)

DR. MARINAC-DABIC: Welcome to the afternoon sessions of the Orthopedic Devices Strategically Coordinated Registry Network Annual Conference.

For those of you who did not have a chance to join us in the morning, just a brief recap. We had a very productive session, focusing on real-world evidence research, in which we featured eight distinguished speakers. During that session, we also had two group discussions, one discussion focusing on gender disparities, the second one focusing on coordination between academic study groups and registries to advance the pediatric and spinal devices research.

Now, it's time to actually kick off our second session of the day, which will be focusing on patient-centered outcomes, and will be moderated by two distinguished leaders in this space, Dr. Sedrakyan and Dr. Devlin.

Dr. Art Sedrakyan is a professor of Weill Cornell Medicine, Director of Cornell's Health Technology Institute, and also the Director of the MDEpiNet Coordinating Center at Weill Cornell Medicine.

Dr. Devlin is an orthopedic surgeon, and Chief Medical Officer in the Office of Orthopedic Devices at CDRH.

So, to kick off the session, we are going to invite our first speaker, Michelle Marks, who is the Executive Director of Setting Scoliosis Straight, a nonprofit foundation that supports the mission of the Harms Study Group. And she will be presenting the project in orthopedics, development of patient and family preference survey aid shared decision making related to surgical treatment of pediatric idiopathic scoliosis.

Welcome.

MS. MARKS: Hello. I'm Michelle Marks, and I'm honored to share our work with you

today on evaluating patient preferences and developing a shared decision aid for surgical treatment of pediatric idiopathic scoliosis. These are my disclosures.

I have dedicated the past 25 years to scoliosis research with the Harms Study Group, and to growing our Setting Scoliosis Straight Foundation, to support scoliosis patients and their families. The work I will share with you today would not have been possible without the collaborative support from our colleague, Dr. Vince Devlin. We are grateful for Dr. Devlin's trust in our study group, and willingness to join forces.

In 2019, a potential treatment paradigm shift was underway in pediatric scoliosis surgery. Instrument infusion surgery, the gold standard, had been successfully performed since the 1960s to correct the deformity and prevent ongoing curve progression. A novel treatment approach where no fusion is performed, known as motion-sparing growth modulation, or anterior vertebral body tethering was emerging at the time. There were limited published results of tethering, and the first HDE VBT device approval occurred in mid-2019.

With this emerging non-fusion surgical correction to scoliosis, our study group sought to understand patient preferences regarding risks and benefits of the AIS treatments, specifically assessing tether versus posterior spinal fusion. Harms Study Group surgeon members collaborated with the FDA patient preference experts to develop a survey tool for patients and families who were considering fusion surgery versus tethering.

From this collaboration, our study group submitted a proposal, and in August 2019 was awarded a broad agency announcement grant funding. This multi-year effort has two phases, the first, to develop and assess patient preference survey results, and second, to develop a share decision-making aid. Both are aimed at comparing anterior vertebral body tethering versus standard posterior spinal fusion for surgical treatment of pediatric idiopathic scoliosis.

This incredible work is happening due to the collaborations between Harms Study Group investigators, primarily Dr. Noelle Larson and Dr. Baron Lonner, and FDA co-investigators, along with patient preference and survey experts and shared decision tool experts. The survey was developed to assess the patient and parent perspective of the risk/benefit tradeoffs with non-fusion growth modulation surgical techniques compared to spinal fusion surgery.

The specific attributes being evaluated are surgical approach, confidence in planned correction, appearance, motion, chance of device failure, chance of reoperation and recovery time. The survey was designed for electronic data capture for patient convenience.

The survey development and pretesting were completed in February 2020. Seven sites of the Harms Study Group were immediately engaged to collect survey data on pre- and post-op patients. COVID-19 definitely limited the data collection in 2020, and even into 2021. But despite these challenges, to date we have collected 326 surveys, 216 being pre-op patients, and 110 post-op patients, of which 65 underwent fusion and 45 had a tether.

In February 2021, Juan Marcos Gonzalez Sepulveda, a patient preference survey expert and collaborator in this study, performed an initial analysis of the survey data. For 183 patients, mean points for non-fusion attribute level are shown in respect to the fusion baseline on the Y axis, and survey attributes are seen on the X axis. These preliminary data suggest that the most important attribute, from a patient's perspective, is post-op appearance.

We will continue survey data collection until the end of this December. We plan to perform the final analysis of the survey data in January, with abstract submissions to the Scoliosis Research Society Annual Meeting, and subsequent manuscript submissions in March.

The second phase of our research effort will be aimed at the development of a decision aid, to be used with patients and families considering fusion surgery versus tether. Collaborator Juan Brito Campana, the Medical Director at the Mayo Clinic Shared Decision-Making National Resource Center, and PI of the Knowledge and Evaluation Research Unit, will assist in this effort using designed participatory action research which is developed and validated by the Mayo Clinic team of decision aid designers.

The first step of this user-centered design approach is to understand how the current decision-making process happens in real encounters between patients, families, and clinicians. Mayo will partner with the scoliosis clinics of the Harms Study Group sites to consent patients and their families, to obtain video recordings of pre-op visits of scoliosis patients considering fusion or non-fusion surgery.

After the videos have been acquired, the recordings will then be observed by Mayo Clinic KER unit. Patterns of patient-clinician conversations regarding treatment options will be identified. Key words, repeated concerns, gaps in knowledge and clinician and patient body language will be noted. After each encounter, the patient will fill out a questionnaire to debrief about the encounter, and will answer questions such as what went well, what was not said, what was important and not addressed. The expert at Mayo will then utilize all this information to develop the first prototype.

Juan's team at the KER will follow the international patient aid standards in their work, which consist of a checklist of content, development process, and ten criteria of effectiveness, such as, the decision aid must provide information about options in sufficient detail, and it must present probabilities of outcomes in an unbiased way that is easy to understand.

The initial prototype will be reviewed and critiqued by both the research team as well as Harms Study Group surgeons and patient volunteers. Their comments will focus on

content, format, language, concerns, clarity and considerations of their values and preferences in the tool. The tool is likely to take the form of prior complex decision aids, since more than one option will have to be presented, and each option has several potential effects that may be important to the patient.

Clinicians from four Harms Study Group sites will be introduced to the prototype decision aid, and trained in its use as a tool for improved patient-clinician communication. We will then iteratively field test the prototype decision aid within AIS patient-clinician encounters and record these encounters. The same questionnaires for patients will be completed using the decision aid and then compared to usual care.

Again, using validated KER unit methodology, the field-testing videos will be observed and the questionnaires will be analyzed, and the prototype decision aid will be further developed based on its performance. The initial version of the tool will be paper based, which will eventually be available as an online tool.

The final version of the decision aid will ensure consensus on the interpretation of evidence-based information contained in the tool. This will be done through a Delphi process, using the surgeon members of the Harms Study Group, and led by Drs. Lonner and Larson, seen here.

The primary goal with the decision aid is to help patients and clinicians together think, talk, and feel through how to decide which surgery is best. In summary, understanding patient preferences and implementing a process for shared decision making will shed light on the challenging treatment navigation. Each patient is unique, and one size definitely does not fit all in pediatric scoliosis surgery. We are honored to do this work, and we are very grateful for the collaborations of our FDA and scientific colleagues.

Thank you for allowing me to participate in this Ortho CRN meeting this year, and for the opportunity to share our exciting work.

DR. MARINAC-DABIC: Thank you very much, Ms. Marks. We truly appreciate your presentation. Your passion for this research and cooperative spirit has obviously led to a very successful stage where this project is currently at.

Before I introduce our next speaker, I'd like to remind all the members that are joining us virtually, all our participants that, please think about any questions, comments, recommendations that you would like to make. The Q&A section is open, and we are monitoring it, so please don't forget to actually send some questions our way.

Our next speaker is going to be Dr. Vahan Simonyan, who is a chief architect of MDEpiNet High-Performance Integrated Virtual Environment. He's also a professor of biostatistics and bioinformatics in the George Washington University. He's going to talk about HIVE data platform that is supporting the entire MDEpiNet CRN architecture.

DR. SIMONYAN: Sorry, I was on mute. Can you hear me?

DR. MARINAC-DABIC: Yes.

DR. SIMONYAN: Okay, wonderful. I guess you see my screen, yes, which says, "High-Performance Integrated Virtual Environment"? So --

DR. MARINAC-DABIC: We can.

DR. SIMONYAN: Yes. Thank you. Today, we have heard multiple very interesting presentations about the precision approach to different ortho devices, how efficacy and safety and other important characteristics depends on the genomic characteristics of the human being, whether sex or gender or maybe mutation-based markers which can define the performance of the device.

So, to this presentation which I am going to give you, it's about the platforms that enable these types of studies, yes. So today, with an advent of precision medicine, we recognize that the personalized approach to all aspects of all chiropractic modalities is usually much more efficient, much more safe. So, the platforms like the one I am going to

present right now are enablers to do this type of study. You know, you have to work with different nature of information, different amount of information. When it comes to genomics, we are working with huge petascale size information. And it is important to have technology that supports you.

The age when we could run our studies in a single Excel file is no more. So, this platform, High-Performance Integrated Virtual Environment is one of those advanced platforms that allows you to do those steps and go further than humankind has ever been before. So, this platform is originated from FDA, and it is the only big data platform which is authorized to operate in a regulatory environment. And it supports the life cycle of healthcare data from real-world data to molecular diagnostics type information.

So, what is it? What it really is, is the functionality to do the following: To get the data from variety of sources. It can be doctor service, directly entered into the web applications that I provide, or patient-reported outcomes. It can be existing data collections. For example, it can be imaging data collections, or EEGs, or ECGs, or whatever type of big datasets already do exist in some institutions. It can be genetic or metabolic, or generally multi (indiscernible) type information which it can directly receive, either from sequencing facilities, diagnostics facilities, from the devices directly.

Or it can also, input can be directly from existing, let's say REDCap, or MyStudies-based registries. So, the first stage is always go and get the data. It can go from some standardized protocols, or it can go through complex handshakes between different institutions, electronic handshakes and APIs, that allows the data to get into HIVE.

And the first thing data encounters is this very secure files, set of institutional policies and techno cybersecurity measures that prohibit any unauthorized access to the system. Then, we all know that data is a wild zoo and there are so many legacy formats, so many types of errors and mistakes, and no standardized approaches in data collection. So

the first thing HIVE does, it provides a set of very important data validation and standardization procedures.

So, since it has been designed at FDA, it has seen many very different types of datasets. So, it's adapted to healthcare data sets, and it knows pretty much all the important data types, how do you harmonize, how do you standardize, how do you make sure that we compare apples to apples and not to oranges?

So, after validation, standardization, the next step is archival. And it is a HIVE honeycomb database system which is an archival system. And that's different from storage, yes. Storage, I dump a file into hard drive and that's stored. But archival is much more. It has to be findable resources that you archive in a federal government ecosystem, for example. They have to be findable, accessible, interoperable, and reproducible. You should be able to access the data in the future. You should be able to search, index data. You should be able to work and you should be able to reproduce the data back an in interoperable fashion.

So, HIVE is also an archival system. So, but also HIVE is a deeply analytical system. Whenever data encounters HIVE, data enrichment algorithms will be run. Let's say it's an image, and we know it's a, for example, breast cancer image. We can attach an algorithm which does artificial intelligent analysis of the image and annotates the nodules, the density, et cetera.

If it's a genomic file, we can run biomarker discovery when the genomic file hits the HIVE. Yeah. If -- so on, so forth. So, it's an enrichment at very high-density analytical core, which has artificial intelligence to statistical to evolutionary algorithm, genomic tools, natural language processing tools.

And the output is -- output usually is in form of some informative, visual, scientific graphs and visualizations, that are easy to operate, and then also it sometimes do active

surveillance pipelines on top of this data and visualizations. So, let's move forward.

What it is, it's a what people like to call to the clouds, but unlike public clouds, HIVE can be installed locally or in public. It has many distributed storage units and distributed computational units, all controlled by one big orchestrator conductor, that allows data and processes to move along computers. And it's accessible through web portal. We didn't want to design a resource that you need to have to be a computer scientist to access the system. We have such important other functions to do. We wanted it to be accessible by web for beautiful visualization interfaces. And the web portal is the way users communicate with it. So, let's move forward.

Like I said, HIVE can be deployed on different ecosystems. There are HIVE deployments today that support registries, and they are deployed in Amazon, or Azure, or a Google cloud. But there are also HIVE systems that are deployed in organizations' local computer cloud, for example, computer clusters. FDA has three deployments of HIVE, and many academic institutions have deployments of HIVE. And it can also be HIVE-in-a-box.

Sometimes you don't want to have too many deep integrations with a particular organization, because their mission is different. You want to roll in appliance into HIVE, as a HIVE-in-a-box, connect it to the network, provide all of the functionality right there within one server, and that provides the same type of functionality, HIVE-in-a-box. Or it can be IO personal notebook.

So, HIVE also has this capacity to work with very many different types of data, but today we heard how people are saying how important it is to enter patient-reported outcomes, or clinical outcomes, or clinical report directly into the system. So, HIVE has this very modern web application framework that allows us very quickly to design surveys and questionnaires, and connect that information, like you treat that information connections to processes.

So, you can have -- the only thing you, the user usually require, is required to do from a list of variables, attach the variables and constraints on the variables, and conditions on which certain patients will be heated, or visible. And by just providing the set of variables, then HIVE is able very quickly to bring up these wonderful interfaces which are responsive design. You take your phone, we recognize and reach environments, patients and clinicians enter this information. They are working in a corridors of the hospital. The lighting is high on this side, low on this side. Sometimes the tablet is held this way, sometimes the other way.

So, the web application adjust the contrast, adjust the phones, changes the orientation. It's designed to be easy to use. And I hope you will have a chance to one day experience that, how easy it is to use HIVE application framework to enter the data. And it's not just a questionnaire. It's a connected set of longitudinal surveys.

This is one of them, that we have designed for stress urinary incontinence ecosystem. When the patient, let's say enters the demographics and preoperative survey, and then after the index procedure, system will call, go back and remind the patient hey, it's time for your 5-week follow-up, why don't you come? And they'll get a text message or an email. Why don't you click here, come and do your next survey, 1 year? It'll be another one, invite, for 1-year follow-up survey, and so on, so forth.

And also, every time patients fills their information, the doctor will be notified, saying hey, patient entered their follow-up, why don't you do your part? So, it's not about hey, can we ask ten questions to the patient. It's about linking longitudinally, collecting the data and interconnected data, so that data can be useful in the future.

So, when we come to patient datasets, it's very important. Security is of ultimate importance, yes, because we are dealing with privacy, controlled information. So, HIVE, in addition to all very important controls like HIPAA compliance, GDPR compliance in this

state, how many serious documents talk to compliance? All types of computer worded things like -- hell, it's a cybersecure system.

In addition to that, HIVE implements extra security measures and extra provenance measures. Provenance through the blockchain, at every transaction as to who, what, when did what with what type of data, is maintained in a blockchain, so it can never be altered. We always know where this thing came from, who got access to what, and what has been done.

And also, we stripe the data into this delocalized ecosystem, we make sure that even protected from insider attacks. You remember the Snowden case or others, yes? Our computer systems are wonderfully protected from the world, but insider attacks always potential issue. So, I am going to run the simulated animation showing how do we do, so even insider attacks are protected from.

So, this is -- let's assume this is a clinical record. It can be from your EMR. It can be from your study data model, clinical trial study data model or any other type of information. Usually in a clinical records database we have many, many records like this. And HIVE is not just one computer. It's many different computers together connected. Yes. So, when the data starts going into HIVE, before entire data is in one node of HIVE, every piece is being striped, encrypted and shipped to one of the randomly chosen locations, unknown locations to the user, as to where that information is and how to decrypt it, is being collected here.

So, the data ends up here. The pointers to the data are ending up here. So, this process continuously goes until the entire data is shipped around and distributed. And then finally, these pointers, which allow us to reconstitute the information is encrypted one more time, encrypted and shipped, let's say to the provenance layer, which can be blockchain or it can be other system.

So, let's go in a little bit more detail into it. So, let's say this is a SDTM data model,

but this is applicable to EMR and others also. So, let's say we have a SDTM data model dataset. Each row represents a patient. Each column represents a variable that codes different patients. And then there are different domains, let's say demographics domain, procedure domain, et cetera. Obviously, you know, now we have like 51 domain in SDTM like data model. So, what we do, we color different rows differently. And because we remember, each row is one single patient.

And we color columns different. Remember, each column is a single variable across the patient. So, what we do, we turn into the mosaic picture like this. No single row is the same color, and no single column is the same color. So, no single patient data is the same color and no single variable is the same color. Why is this important? Because then we start shipping different colors to different locations, by which doing, no two different colors are in same location.

And by doing so, we guarantee, in an unlikely and never happened before situation, that one particular node got compromised, they cannot recover even a single patient data, and they cannot recover even a single variable data. And by doing so, we ensure that the only way, which never happened before, to get access to a single patient data is to hack all ecosystem, including all computers in a blockchain in all (indiscernible), et cetera. So, this is, actually it shows that this is going much beyond what other (indiscernible) ecosystems are providing today.

So, let's move to the other aspect, visualizations. HIVE doesn't just give you text information backwards. It also provides you this very interactive, three-dimensional, or sometimes even four-dimensional dynamic visualizations that allow you to interact. You point your mouse; it shows more information. You click, you jump to another drop. We believe that real science is not done by reading the tape. It's done by interacting with a visualization, beautiful scientific information that it is.

So, in HIVE, everything -- the front end is visual interfaces for entering data conveniently. On the back end, on the final end, we have these nice graphs and demonstrations and things that allow to interact with the data. So, what is important when we're designing our HIVE? Why the ecosystem should be chosen for a particular goal? Very important, capabilities. Does your system provide the functionality I need? Scalability, does your system provide me to be able to get more data, vertical scalability, and more types of data, horizontal scalability?

Does your system -- is your system sustainable? Does it depend on one participant, which tomorrow goes out of business and that's it? Or is there support in government? Is there support in commercial and academic points? So, HIVE, in that sense, is supported by government, by commercial enterprises and by academia. And then robustness, all codes break. We all know that. We constantly fix bugs and things like this. How long your system exists? How many times it has seen different situation where it has been stressed, et cetera? Robustness.

HIVE has been used for about 15 years already in very complex scenarios. Compliance, security compliance, privacy compliance, HIPAA, GDPR, you name it. Yes. High interoperability. Can your system work with other systems, either by code interactions or by composing, importing, and exporting interoperable data types? So, these were the considerations that we took very important, very carefully in order to design our HIVE system, to provide solutions that enable our scientists to do really cool types of research, where we can link genomics and the behavior of devices in human beings. Thank you.

DR. MARINAC-DABIC: Thank you, Dr. Simonyan. Thank you very much for this great journey through the HIVE.

Now, we're going to slightly move the actual, our journey to a different area, where you're going to welcome Dr. Bilal Chughtai, who is associate professor of urology at Weill

Cornell Medicine, who will be presenting on using patient-reported outcomes and electronic case support forms in routine practice to advance research and surveillance. And he's going to use a case study in women's health. Again, we would like to learn from other critical areas and apply them to the field of orthopedics.

So welcome, Dr. Chughtai.

DR. CHUGHTAI: Thank you for the opportunity to present today on using patient-reported outcomes and electronic case report forms in routine practice to advance research and surveillance: Case study in women's health. These are my disclosures for my presentation today.

Today I am going to review our project on women's health. Our objective was to develop an app that enables collection of patient-reported outcomes in stress urinary incontinence for women's health. This is our team that helped support and complete this project.

Stress urinary incontinence is a common condition affecting one in three women with an annualized cost of over $20 billion. There are nonsurgical options with variable success. These include Kegels, biofeedback, and other nonsurgical options. There are numerous surgical treatment options, and the literature describes over 200 treatment variations. The broad categories include bulking agent, which fills the urethra to stop or limit incontinence, abdominal procedures, which support the urethra to restore its natural anatomic position, and sling procedures, which support the urethra from below, to help kink the urethra during strenuous activities or times of abdominal strain.

Mid-urethral slings are the current gold standard for stress incontinence, with 99% of urogynecologists using them in their practice. There are numerous short-term studies on their safety and efficacy but limited long-term data. Further, there are over 70,000 lawsuits on transvaginal mesh products, with most of them being on slings.

We have previously conducted a study of the graduating loss of resonance, and found mid-urethral slings are the dominant procedure. The number of traditional procedures fell from 17% to 1%, mostly replaced by mid-urethral slings between 2003 and 2012. We know short-term safety and efficacy but need long-term patient-reported outcomes following sling procedures.

We subsequently conducted a study looking at the long-term safety with mesh implants for stress incontinence between 2008 and 2016. This was a study looking at New York state resident female patients undergoing surgical stress incontinence, using ICD-9, ICD-10 codes to identify those who had a mid-urethral sling alone, mid-urethral sling with abdominal repair, and mid-urethral sling with transvaginal repair. Patients who underwent concurrent mesh-based transvaginal repair were excluded, and patients who went a previous sling or prolapse repair dated all the way back to 1995 were then excluded as well.

In our long-term study, we found the mean age for patients was 53.7 years. Median follow-up time was 4.8 years, with follow-up as long as 6.8 years. The type of sling operations included 77% that were isolated mid-urethral slings, 20% that included a concomitant transvaginal repair, and 3.2% that included an abdominal repair.

We found that risks at 7 years post mid-urethral sling surgery included a 3.7% risk of erosion, with a higher risk in younger patients, lower volume facilities, and a history of hysterectomies. We found a 6.7% risk of reoperation in those with concomitant abdominal procedures. Those with a previous hysterectomy, as well as those with a diagnosis of depression were found to have this higher rate of reoperation.

As we can see from this data, there's clearly lacking information on patient-reported outcomes. The events collected were either return to operating room or a diagnosis of mesh erosion. So, we wanted to create a user-friendly, secure, patient-facing mobile app that can enable data collection, and one that can facilitate monitoring of long-term follow-

up critical events to assess efficacy and safety, and it also needs to be integrated with a physician data collection, to solve (indiscernible) problems when it comes to high attrition rates with studies that have previously been done on stress incontinence in women's health.

The goal of the women's health CRM is to collect a minimal dataset, taking less than 5 minutes for initial data, and 2 minutes for follow-up data for both patients and surgeon. This data can also be managed by a non-HIVE registry as well.

We subsequently tested our mobile app, and almost all providers and patients found the experience positive and efficient. Patients rated their experience as 9 out 10, with 100% finding the questions clear, understandable; 95% found the layout convenient; 100% found the text, colors, contrast effective; 65% found it was intuitively clear, and 95% did not need help to complete it. And over half the participants were interested in possibly replacing in-person visits with this type of mobile application.

Providers found the experience, at 8.6 out 10, 100% found the questions clear, 100% found the layout clear, 80% found it intuitively clear, and 80% were interested in a method to possibly replace in-patient visits as well.

This mobile app overcame the limitation of administrative datasets and may also help address limitations of both retrospective studies and administrative dataset studies that either have high attrition rate, or typically are able to just find composite endpoints. With this mobile app, these factors no longer bind data to the capture process. It includes again, security, and provenance, including blockchain and ease of access as well.

Our study on the usage of this mobile app has already been accepted and published in the *Journal of Urology*, and now we have adopted this app for use in all stress urinary incontinence cases at New York Hospital.

Thank you again for allowing me to participate in this meeting.

DR. MARINAC-DABIC: Thank you very much for excellent presentation. Again, that one is in particular interest because it features one of the NEST-funded projects, which have been done in collaboration with MDEpiNet, so excellent work, that we had the chance to actually learn from.

And so now welcome to our next speaker, Dr. Noelle Larson, who is the associate professor of orthopedics, director of research for the Division of Pediatric Orthopedics and Scoliosis, and pediatric orthopedic surgeon at the Mayo Clinic. She will be presenting on potential role for mobile applications for collection of patient outcomes, and development of patient application for pediatric scoliosis.

Welcome, Dr. Larson.

DR. LARSON: Thank you. It's really my pleasure to be here today, and to learn from these other groups who are potentially a little bit further along in this journey. I do have some research funding and disclosures.

Again, I feel like this is really fundamental to my role, but I do surgeries, I take care of patients, I do bracing and nonoperative care. But at the end of the day, we want to make it better for the next generation. And from my standpoint, that involves a lot of critical evaluation of what we're doing, and again, looking to the next step as to what we can do for our patients and make care better.

In general, a registry is great because it's not interventional. It's an easy sell for the patients, and they're generally willing to participate. I think some of the problems are the back side work, as far as abstracting minutiae from the clinical record, manually uploading patient-reported outcomes. And currently a lot of our work is very high quality in pediatric orthopedics and scoliosis, but it's very granular and labor intensive. And so that's why we're really looking to new technology to make our work more efficient.

So, an example was a long-term follow-up study I completed. I started it about 10

years ago, and again, very slow work finding these patients, bringing them back, very rewarding. I still have this patient's Milwaukee brace up on my shelf up there. I don't know if you can see it, but I've got my patient's Milwaukee brace that she brought back 30 years later, after having been treated at our center.

But how do we keep track of patients for 20 or 30 years after their index treatment? It's not really feasible to bring hundreds of patients back. Can we keep track of them potentially through these mobile devices? And again, to complete the study, which again only had 50 to 60% follow-up at 30 years, it was me sitting on the telephone, my study coordinator sitting on the telephone, mailing out-patient-reported outcome folders.

So more and more so, as we've heard today, we live our life online. We order our food; we do our banking. We also are very secure ordering things with a credit card online. We connect with others, and I think we've seen the benefits and the dangers, but how do we harness all these social networks and a high level of computing power as well, to make it practical and useful for research? Again, 170 million Facebooks views in 2019, and if anything, we're living more and more of our lives online now, secondary to the pandemic.

The average American spends, again nearly 4 hours a day on their phone, and I would think the average teenage girl is upwards even higher of that. And for a lot of time, for scoliosis, that's who we're trying to reach.

Mobile devices are changing science, so I participate in the eBird app study, and this app collects 120 million observations per year. It's really revolutionized a lot of the science of birding, because they get lists of cases of bird spottings all over the world, in real time. And they have been able to again develop computing power to process this data and turn it into useful research.

Now, some people are bad birders, like myself, and I probably misidentify a bird here and there, but because the volume is so high, those missed sightings are going to be, you

know, noticed. And in addition, because as soon as I post my crazy bird sighting in Rochester, Minnesota for a bird that only exists in Brazil, you know, all the other birders are going to come out and look for my bird and see if they can find it, which they probably won't be able to.

So, the thing that's cool about these type of apps is it gives something back to the user. So, I can keep a life list of all the birds that I have seen. It has automated birdsong ID. It has automated bird photo ID. I can talk to other birders. Again, if somebody posts a cool bird in my area, I can run out and go find it. And then these huge datasets that are becoming available are available to the public. So, I can go on and download, again those hundreds of millions of views myself and do whatever I want to do with it, but it's not protected, right.

So, how do we do this for humans, and for children? A lot of these things that sound cool for birds are not so cool for humans if we're talking about digital voice recording and location trackers, and how do we make this safe for our patients and families and make it so they're comfortable using it? Another question, really, is that of diversity and racial equity and socioeconomic equity. I mean, not everybody has access to a phone. And how can we, you know, make this so that we're capturing a full cross section of society?

And then, people aren't going to do it unless they have something that's being given back to them, right. For this eBird app, I think it's kind of fun. The interface is nice. Again, I can communicate with other birders. So, whatever we develop also has to give something right back to the patient, so that they are feeling like their time is worthwhile, whether it's tracking their outcomes over time, whether it's putting them in contact with other people who have the same condition, whether it's making it easier for them to access their healthcare providers. There has to be kind of a two-way street.

I think this has been really nice done for Parkinson's, as one example that I've looked

into, and you've heard of a lot of other great examples earlier today in the session. But again, particularly with some of these smart phones, we can capture real-time data about mobility, which is super important for orthopedics. We can also capture again, change in time over whatever parameters that are that we are measuring, particularly if we have that patient buy-in and they feel like this is part of their healthcare plan.

So, for scoliosis, the immediate opportunities I see is that we could reach patients of different ages, we could reach patients with a variety of curve severity. Historically, we weren't bringing people back in with mild curves that much. We just kind of assumed they're going to do fine for the next 50 years, and who wants to put them through the risk of an X-ray. But again, maybe there's other ways that we can study patients over time with more mild disease.

Historically, it's been hard to differentiate between mild, moderate, and severe scoliosis in adulthood, but again, if we have a larger dataset with different time points, with patients who have surgery and bracing and nothing, just observation, again I think it's going to give us enough data maybe to answer some of these questions about how we should care for these patients.

And then for the patients who do require surgery with severe curves, it gives us a way to monitor them before the surgery, after surgery, and also the impact of any complications which may ensue. And again, the goal really is to have a shared dataset that both the patients and the physician can use, kind of a portfolio of outcome over time.

This is specifically critical for pediatric scoliosis right now because we have several new devices on the market, and these are approved through a humanitarian device exemption which shows safety, but the efficacy and the comparative data regarding how these devices fare, long term, compared to fusion are still pending. And I think, because we're trying to preserve growth, we're trying to preserve mobility, truly these like health-

related quality of life and mobility measures are going to be really critical to figure out the role of these new devices.

So, what have we done so far? I have a REDCap survey, which is fairly basic, but is open currently at Mayo, where patients can log on, and they don't necessarily have to be Mayo patients. Any patient who attributes scoliosis, or claims to have scoliosis can click this consent button, and log on and complete a Scoliosis Research Society questionnaire. The problems with this is REDCap is relatively bland. The user is not getting anything back, and they're just doing it out of the goodness of their heart. But it is secure, so that's helpful, and there's no independent validation.

Again, kind of like my Brazilian bird that I saw in my backyard in Rochester, Minnesota, there's no real validation that the patient actually has scoliosis, but you hope the number of misdiagnoses are relatively low. And then again, there's no X-ray data, you know, that you can collect on your phone at this point. And the positive is, you can reach many patients, it's convenient. It's low cost. We can follow people longitudinally. And again, with respect to these new devices coming out, there may be a way we can figure out to link this to the device for surgical patients and link it to the UDI.

So, we've been working closely with the FDA, and with Dr. Devlin, and CAPT Peat, and looking into what kind of prospective data collection we can do in partnership, as far as collecting health-related quality of life. We'd like to make a more visually appealing app that could potentially capture longitudinal follow-up. And then, at some point, it may not be on the first iteration but at some point, we have to give that end user benefits to maintain interest and engagements for our patients.

So, at the end of the day this meeting is so powerful, and I truly believe this is our future, as far as somebody having a study coordinator independently typing in patient attributes into a centralized registry. I mean, we need to move beyond that, and those

registries are extremely valuable for the granular data, but we also want to be capturing more patients at lower cost. And that is really a powerful partnership between the administrative data, the detailed registries that currently exist, and then hopefully some of these ways to capture real-world data via aps.

So, thank you for your time, and I'm really looking forward to this discussion. It's been a great day so far.

DR. MARINAC-DABIC: Thank you very much, Dr. Larson.

We've heard these three extraordinary talks, and I would like now to ask our moderators to lead a discussion about the next steps with mobile applications.

DR. DEVLIN: Good afternoon. It was a wonderful series of talks about the future and the present, which are emerging very quickly. I had a question to start off, with -- directed to Michelle Marks.

There has been excellent progress in the patient preference survey completion, so that project appears nearly finished, yet the shared decision aid project is taking off, and at the early stages. Are there any takeaways or lessons learned from the patient preference study that you see relevant to the shared decision-making tool?

MS. MARKS: Yeah. I think that the survey information is really going to inform the content of the shared decision-making tool. As the preliminary data that I shared showed, appearance is an important attribute to patients that we're seeing in their decision making between fusion and non-fusion treatment. It definitely should be a component that's discussed as a consideration when the decision-making tool is developed, for sure.

DR. DEVLIN: Thank you. Moving on, when you -- go ahead, Paul.

MR. VOORHORST: Yeah. I had a question for Dr. Simonyan. You know, HIVE seems to be a highly interoperable data collection methodology with promising cybersecurity features. Can you expand on the advantages and disadvantages of HIVE compared to the

many different types of orthopedic registry efforts, some of which have been going on for decades?

DR. SIMONYAN: Wonderful. Thank you for the question. Yes, I can. So, you know, it's -- when you are starting something new, you always go through the stage of learning and making mistakes and fixing. So, by being pretty late in this role, we had advantage of, you know, learning from other mistakes that had been done before us. So, we could afford to be innovative and come up with these new data types and new interfaces while learning from the others and not making the same set of mistakes.

But also, I'm going to, I'd like to mention a few kind of things which are different in our ecosystem with relation to others, yes. So, in HIVE we support very complex data entry branching logic. So, when you answer a question, based on that question, we either will ask the next question or skip that because it's irrelevant. So, we can build -- the branching logic of the questionnaire can be much more advanced than, for example, the REDCap or MyStudy app or other registries most of the time.

Also, we support such things as precomputed variables. You fill your weight; you fill your height. It immediately computes the BMI. We can actually have precomputed ranges of constraints of the variable. We can have arbitrary transformation units of measurements, which will system automatically switch, allow you to switch between different units and do the (indiscernible) itself.

We can have unlimited number of entries for multi-value variables, yes, how many visits are there, what are the drugs, the number of drugs. It's all unlimited. The most other registries, which are usually SQL based, they have a prelimited amount of information that you can enter, yes. We have such things as two-dimensional image-based entry where you click on an image to enter the variable. You are sent here, where the surgery took place. Or we can also have three-dimensional image where you rotate the image, click here, this is

where the, you know, the annotation is.

And we also support blockchain integration. No other registry in production, as we know, supports blockchain integration for (indiscernible) and provenance. Well, our security and permissioning layer is much more complex. You saw, I demonstrated few of them. And we also support something like data in storage encryption and in-transit description (ph.).

When your computers talk to registry back and data is always encrypted moving between them, or even your computational algorithms talk to the data, data is encrypted between them. Most registries that we know of do not support that. Yes. Only one very important characteristics, our HIVE servers have gone through security requirements that are compliant with government ATO process, authorization to operate in a (indiscernible) environment. No other server, and no other ecosystem has gotten that. Yes.

And also, the dictionaries, for example, in other systems, when you are constraining your variable input to a dictionary, we can say it can only have this, this or this value. For our case, dictionaries can be dynamic. We can, quote, link to the external resource of ICD codes, LOINC codes, the cancer, and disease annotations, resources, et cetera. So, in a way, our questionnaire is this distributed questionnaire, where we fetch runtime. We can go and get the information (indiscernible) as the person is trying to fill in, et cetera.

So, there are many other features, like the way we interact with the different types of information. We support EEGs, ECGs in your questionnaire, can just pull it up and look at it, yes. We can bring up a DICOM image, where you can scroll your mouse and look at the different cross-sections of your image. And so, our system is integrated with relation to other types. Let's say you are running a REDCap or MyStudy, it will support your questionnaire, but the moment you want to bring the ECG linkage to it, you have to use some other tool. Or the moment you want to see a list of biomarkers that, let's say genetic

studies have been happening, then you have to integrate with some other vendor. And that's a problem when you're running a registry, when you have to link and work with many other contractors to provide one single integrative functionality.

So, that's an advantage, yes. These advantages, that all platforms have advantages. It has advantages. HIVE is new, and some of the researchers are not yet completely familiar with it. Hopefully we are coming with FDA background, so the trust is usually not an issue. But there is a need for us -- this is a wonderful tool we are trying to leverage in as many places as possible. And it is a disadvantage of being the last one in the list, in a timely manner, in a time manner, so for us to do some marketing, teach our users how this works, and things. But this is an ongoing work they are trying to do.

They are not perfect platforms. They are just good for a purpose, and we are trying to build the one which is good for many purposes that we need to.

DR. DEVLIN: Really appreciate that explanation. It seems like a very flexible and capable system and looking forward to learning more about it.

MR. VOORHORST: Thank you so much. Thank you.

DR. SEDRAKYAN: Maybe I can answer -- oh, go ahead, Paul. Sorry.

MR. VOORHORST: No, no, go ahead. I was going to -- yeah.

DR. SEDRAKYAN: I was just going to ask Dr. Larson if she will be open to collaborating with HIVE, because she's done a tremendous amount of work already, thinking about this PR role measurement in scoliosis, and launch something with HIVE in collaboration, which would be much more generalizable and open to many, many patients, internationally even, potentially, because of GDPR compliance that HIVE offers.

DR. LARSON: It'd be fabulous. Yes, please. I'll try and get your contact information and I would love to collaborate. We're actively looking for partners to collaborate with.

DR. SIMONYAN: Wonderful. Thank you. We would be delighted. And we can

organize a separate meeting.

DR. SEDRAKYAN: Back to you Paul, sorry.

MR. VOORHORST: Yeah. No, thank you. I have a question for Dr. Chughtai. You know, it seems like there is a highly successful adoption rate of your mobile app in collecting patient-reported outcome measures in your study. Do you recommend the strategy of exclusive use of that type of electronic, you know, data capture and case report forms, or a hybrid strategy that combines more traditional data capture methods with electronic data capture?

DR. DEVLIN: Bilal, you're on mute.

DR. MARINAC-DABIC: Maybe someone else from the team, like Dr. Sedrakyan, may answer.

DR. SEDRAKYAN: I'm happy to answer. Bilal and I are co-investigators on the project that he launched. And the ability for us to leverage any electronic data is certainly something that is logistics aspect, rather than technology. HIVE allows us to get all of that information in a very seamless fashion, grained into the like local HIVE-in-a-box that we created. But there are certain, of course, like certain aspects that are logistics related, collaborating with an institutional IT team and many other issues that take time to resolve.

And when you try to launch something on a much higher level, like nationally, unfortunately we have to deal with each institutional IT individually. That's the main challenge of trying to integrate EHRs with the patient-reported outcomes right now. And ability to bring like data in, like REDCap has ability recently, like some fee-based system that they can integrate, but it still takes quite a bit of time to create that and be able to integrate electronic health record data into the same place where you can collect patient-recorded outcomes.

MR. VOORHORST: That makes sense. Appreciate the answer.

DR. DEVLIN: Thank you so much. I had a question for -- actually a two-part question for Dr. Larson. The first was, based on your interactions with the patients that you treat who come to you from across the United States and the world, what have you seen as the greatest barriers that limit their participation and the participation by their families in the research studies that you're involved with?

DR. LARSON: That return to follow-up is challenging. I would state that has been a silver lining to the COVID cloud, is allowing us to do virtual visits, and mailing of the radiographs. The families love it, you know, and on a single day, I'll talk to a family from Nebraska and Kansas and Chile, this week. I've done virtual visits. And again, they understand they have to come back if there's a surgical complication, but it has really allowed us to talk to patients from all over the place. And if there's a way again to integrate high-quality data collection in the virtual platform, that would really improve our follow-up.

DR. DEVLIN: Thanks. The second part of the question I had was related to your work having to do with tracking -- not tracking but interacting with patients who are involved with different social media platforms. Have you encountered limitations, and any logistical problems, and if so, how have you dealt with them?

DR. LARSON: Well, it's delicate, right. And a lot of these social groups are patient support groups, so they do not really want physicians and surgeons on those groups. I think there are certain leaders, Curvy Girls, some of the folks involved in the Facebook user groups that I have been in contact with, we've kind of met at meetings and developed networks. Our Scoliosis Journey REDCap platform, we have not advertised yet. So, we got IRB approval about a month ago. And I am still kind of beta testing it, before we truly launch it, so open to feedback.

But again, there is a little bit of bias, and even with our, the shared decision-making process as well for Michelle Marks' project, there's a little bit of bias. I mean, if you reach

out to the people that really like the new and cutting-edge devices, you're going to hear something different than if you reach out to groups of people that are in the 20-year outcome fusion support group.

So, I think there are tricky problems with the virtual world, and how do we make it equitable and accessible to all in a uniform fashion. So, I think we'll lean on this group here, who has more experience, potentially.

DR. DEVLIN: I think those are all great points, and thank you for sharing your work, which is very pioneering in this area.

CAPT PEAT: This is CAPT Peat. I wanted to interject really quickly. Thank you so much for the presentation, and I wanted to just direct my comments to Dr. Larson, Dr. Sedrakyan as well as Dr. Simonyan.

We are currently working on our medical device app, and this is on concert with Dr. Larson where this was developed. So, we are already going to be liaising as a group, to be able to flesh out that particular app and making sure that we're collaborating. So, I just wanted both of you, all of you all to know that that is already in the works, and that is something that's FDA funded. So, I do think that this is the right conversation, particularly as Dr. Larson just mentioned, when we talk about access, making sure that it's accessible to all.

DR. SEDRAKYAN: Oh absolutely, CAPT Peat. I mean, that's why I asked the question, because absolutely, we can't build this in separation. It should be done in collaboration with groups that have experience, and also folks who are potentially users.

And just going back to Paul's question, I think one aspect that HIVE solves really well is collaboration between physicians and patients. That environment that is set up, that questionnaire sent to a patient triggers also, it can trigger a questionnaire to a doctor. If patient's filling out the information, they're fully protected, and they can also mention

which doctor can see their record or their answers, it creates like this environment where there can be also a patient preference assessment.

So potentially, the patient preference tools that Dr. Marks was talking about can also be integrated in such environment that there is a back-and-forth communication and better understanding with -- sometimes these in-person visits are very difficult or talking over the phone is -- even that is relatively complicated. Capturing this in a scientific way, and in terms of questions and answer and the responses, creates this nice collaborative environment that, as Bilal Chughtai highlighted, allows physicians to monitor how patients are doing, can forego 80% of their in-person visits.

This is really important in terms of efficiency and also care delivery. I just wanted to highlight that aspect. I think this can trigger really nice collaboration in pediatric scoliosis community.

DR. CHUGHTAI: Appreciate those comments. It all sounds very promising, and hopefully increases better collaboration with patients, their caregivers, and their surgeons. Thank you.

DR. DEVLIN: All right, well I'd like to thank everyone for the excellent presentation and great discussions, and for giving us a little extra time to hear everything. And with this, we'll close this section and move on to the next topics.

DR. MARINAC-DABIC: All right, so thank you very much, Dr. Devlin.

I want now to introduce CAPT Jonathan Forsberg, who is an orthopedic oncologist and a clinician scientist who practices at the Murtha Cancer Center, the National Cancer Institute, and Johns Hopkins University. He will present on the development of a patient-reported outcome measure for use in relation to osseointegrated prostheses. I just saw Dr. Forsberg on the screen, but then I saw him disappear, so I hope that he's still on.

CAPT FORSBERG: I'm here. Can you see me?

DR. MARINAC-DABIC: Yes. I can see you now.

CAPT FORSBERG: Okay, good. All right. Well thank you very much. I very much appreciate the invitation to give you an update on what we've been working on.

I presented this a few years ago, in the context of the Osseointegration Quality Registry, and now we actually have some patient-reported outcomes to show and compare. And transdermal implant surgery is new and exciting. It's a field of orthopedics that hasn't really been characterized. So, we felt the need to get the experts from around the world to contribute their cases to get a handle on the complication profiles so we can identify who can benefit and also expand this to other indications if safe to do so. Next slide, please.

Of course, I'm a government employee, next slide.

I do have some disclosures. I'm the principal investigator of both studies that I'll discuss today. One is an FDA early feasibility study in humeri and then the transdermal application study, and I do receive some research support from Zimmer Biomet and consult in this space. Next slide.

So, in the United States, we have three implants available. Only one is FDA approved at the current time, and that's the OPRA Implant System on the left, and that will be the focus of today's discussion. Next slide.

So, as we look at transdermal bone anchor devices, we have to ask ourselves, what the heck is normal, and what the heck is abnormal? And the slide on the right is pretty much abnormal. And then we have varying degrees of normality. But what impact does this have on patient satisfaction? We know -- yeah -- next slide.

So, we're conducting two clinical trials funded by the Defense Health Agency, and both, I'm proud to say, have completed enrollment. First is the early feasibility study I discussed and the second is the transdermal amputation osseointegration study. And we're now in the follow-up period for both studies, but I can share some interim data with you.

Next slide.

In 2017 we recognized that if we were going to figure out some of these questions, with respect to transdermal bone-anchored implants, we would need a team of international physicians using a variety of implants. So, we devised an international registry to correct -- or to collect a variety of information. Next slide.

And this allows us to present our study demographics within the context of a background. Next slide.

Of registry data from around the world. And what we can see right away is our military patients are younger than the international patients, which is not surprising. Most of ours are young, active-duty service members. Next slide.

Most are less than 10 years from amputation. Next slide.

And our -- and this follows the distribution on the world stage. And you'll notice an Integrum symbol in the lower right-hand corner. This just designates the manufacturer of the implant that we're using in our trial. Next slide.

Most of our patients are male, as you'd expect. Next slide.

And the mechanism of injury is by far most prevalent in the blast injury patients. Next slide.

Most of our patients are unilateral, although we do have several bilateral lower-extremity amputees, and some triple amputees, all of -- and each of the triple amputees have had osseointegration on all three limbs. Next.

So, let's talk about the femurs first. Next. Next slide. Good.

So, the QTFA score -- most of you are saying, what the heck is the QTFA? It's the only validated score for use in transfemoral amputees who've had osseointegration, but it's exceedingly cumbersome. It's about 30 pages. Patients hate it. Our research assistants hate it. And we're looking toward more efficient ways of garnering the same information.

But what we see is better function after two years, and fewer problems. The problem score is in the light blue, down below. Next score -- next slide.

We see no significant improvement in walking aid, which is surprising to us, but we did see a significant improvement in walking capabilities and walking habits. It's easier for patients to walk with osseointegrated implants rather than a socket. It takes them fewer, or less time to get up and go, so to speak. Next, next slide.

There is no significant difference in pain interference, but we'll talk about pain behavior in a second. Or I'm sorry, the other way around. We'll talk about pain interference in a second. So, we questioned whether we should collect pain behavior in the future. Next slide.

But we did see a significant improvement in physical function, shown here in the purple line. Next slide.

So, in the OPA score, we did -- patients reported using their prosthetics more often, since it's easier, and for, also for longer periods of time, since they're more comfortable. But we did see, in a ceiling effect, for days to week use, and hours per day use, for about 12 hours a day. So, our patients are wearing them pretty much all of waking hours. Next slide.

But we found no improvement in health, quality of life index from baseline, and it's plateaued for, at about 6 months. Next slide.

The functional status measure improved, and also, as did the satisfaction with the device and services. And these are, we'll see if this is durable over longer than 24 months. These patients are early adopters, and they go through the honeymoon period pretty quickly. Then they start to discover the rate-limiting step, or the rate limiters in this equipment, like the fail-safe, for instance. We'll talk about that in a little bit. Next.

So, I want to talk just a little bit about composite outcomes. You know, we were, we weren't sure if the promise was going to win the day, in terms of patient-reported

outcomes, but as a surgeon, what I really want is I want less pain, and higher function. I also want patients to get out there and do the things that they want to do. So, by multiplying use time and physical function, we get a composite outcome, and the results are fairly striking here. Next slide.

And by the same token, if we look at function, more function, and less pain, by simply dividing physical function by pain, we see a pretty nice trend here. And we think that this may, in fact, be used to power further studies investigating transdermal implants. Next slide.

So, you can't talk about transdermal implants without also talking about soft tissue infections. It's my opinion that this is just simply the natural history of the transdermal system. We found that most infections, most first infections occur during the first 5 months of an -- I'm sorry, 5 months of surgery, rather, not 5 months of injury, 5 months of surgery. And the risk factor for multiple surgeries is age and BMI, because most of our efforts at osseointegration are geared toward minimizing motion at the aperture. That's where the abutment protrudes through the skin. Next slide.

In terms of the humeri -- next slide -- the results are about the same. We didn't see any difference in the PROM score at any time period. But keep in mind, we're look at an early feasibility study of 12 patients. Next slide.

We did see a decrease in the DAS score, although this was not statistically significant, probably because our time-zero confidence interval is so large. You know, there are so few patients with transhumeral amputees willing to undergo osseointegration, and some are -- some never wear a prosthetic, and some wear their prosthetic all day. So, it's difficult to draw any conclusions. Next slide.

But I will say, the mean hours of prosthetic use per day increased dramatically and that mean days of prosthetic use per week also increased dramatically, but you'll see a tail

off on the right curve, and that's due to COVID. Some of these patients became unemployed during that time and didn't need to wear their prosthetic. Next.

I'd like to thank everyone for their attention today. I just wanted to say, we have not had any adverse events related to the upper extremity prostheses thus far. That's why I didn't include any Kaplan-Meier curves, but we know they're probably coming. But no infections in the upper extremity at all.

So, happy to take any questions. Thank you.

DR. MARINAC-DABIC: Thank you very much, Dr. Forsberg. We will have the questions in a bit, after the actual additional speakers, but if you can stay around for that part, that will be great.

I would like now to introduce Dr. Jialin Mao, who is the assistant professor in the Department of Population Health Sciences at Weill Cornell Medicine. She heads the analytical core of the MDEpiNet Coordinating Center. She is a physician and epidemiologist by training, and she will be presenting on ICD-10 and claims data used for outcomes research.

DR. MAO: Thank you, Danica.

Thank you, everyone, for having me here to talk about this issue today. Actually, many of you have heard the presentation warning, so you have seen that we have already capitalized on the ICD-10 and are making use of it to study gender-specific outcomes in hip and knee replacements. I am going to give a more conceptual level introduction to this, so that you understand how this has helped us in those projects. Next, please.

The current state of our outcomes research in orthopedic is nothing new. Many of you must have come across studies like this in previous literature search or in your work. For example, this one looks at risk-adjusted hospital outcomes in joint replacement procedures. This study looked at the 12-year risk of revision after primary total hip

replacement in Medicare. This is actually a quite intriguing topic, and I'll come back to this later. Next.

So, this study looked at implant-related complications in all patients with opioid use disorder, all in primary total hip replacement, in Medicare as well. Next, please.

So, U.S. actually changed from ICD-9 to ICD-10 coding system in October 2015. A few other countries actually switched a bit earlier, so we have been facing this challenge a bit longer than other people. So, one of the biggest issues is laterality. We all enjoy the benefit of having to have two hips, two knees and two ankles, but that actually does create some complicated issues for us in research. For example, in ICD-9, there is no laterality of the hip and knee -- of any replacement. So, it is just total hip replacement, or total knee replacement. Next.

So, for example, in this study, when they looked at 12-year risk of revision after primary total hip replacement, what did they do to deal with the bilateral issue? So, what they did was that they sent their patient, if they have a second primary procedure coded, during that second primary procedure would be on the other side. But then this could create a selection bias. What if those people who have bilateral procedures are at a higher risk of revision, and you lose those patients?

And as we all know, the mean age of patients getting total hip replacement is about 65. So, what if they have been -- there has been a primary procedure on the other joint before the index procedure? Then we would never know, and we couldn't adjust for it appropriately. And this, the revision procedure might be actually identified on the other side that has been reported earlier, and you've mistakenly taken it as the one that you identify in Medicare. The second issue is the lack of specificity. Next, please.

So, as we all know, this -- as I was saying, the total hip replacement procedure code is just one code. It was total hip replacement. So was total knee replacement, and total

ankle replacement, and there was no granularity about that. And the thing you want to study, you can only study it on a procedure level. Next. Next, please.

Also, in terms of complications, there is nothing more specific than like mechanical loosening of prosthetic joints. So which joint was it? Is it a knee? Is it a hip? We don't know. Is it a left, or right? We don't know. So, this could lead to -- next, please.

This could lead to a misclassification of the outcome. Next, please.

The question now is that can ICD-10 help us? We all know that, if you have worked with ICD-10 before, you will know that the code was really exploded, especially the procedure code. If you have one procedure code in ICD-9, you now can probably translate it to one in 10, the ICD-10. But that does give us a lot more granularity on the procedures and complications and other things that we want to identify, and there are some benefits to it. Next, please.

So, first of all, in terms of laterality, instead of getting one overall code for hip replacement, we now get two sets of codes, one for right hip replacement and one for left hip replacement. For a procedure for a prosthetic-related complication, it is also distinguished between right and left hip joints, fracture, or no. So, we are now able to more clearly identify which one was the one that was operated on, and which one was the one that had the complication. Next, please.

And that actually gets us a lot of (indiscernible) on flexibility. For example, we're able to -- you can do a limb level analysis, focusing on the joint, or you can do a patient level analysis, focusing on a patient. And you reduce the chance of having misclassification. And we also reduce the chance of having selection bias because we don't have to exclude anybody just because they had two procedures, and we can adjust for it accordingly. Next, please.

And then, there's also more granularity to the code. In addition to having just right

and left, the sixth digit actually tells us about what type of implant it was using, whether it was metal on metal, metal on (indiscernible) ceramic or ceramic compilation. The seventh digit tells us if it's a cemented prosthetic, or uncemented. It's obviously not perfect. In some cases, it was coded as unclear. And you will see that when Per-Henrik will present a study in which we actually capitalize on this information. Next, please.

So, this gives us the power to ask more specific study questions. Instead of just asking questions about the procedure outcome, now we can go down a bit to device type. So, in addition to what we -- it's a lot more specific than -- well, it's not perfect, but it's a lot more specific than what we had before. Next.

For outcomes, we also have more granularity now. For example, we now can tell if it's a hip fracture, a knee fracture or ankle fracture, whether it was on the right or on the left. So that really reduces the chance of having a misclassification of your outcome. We can now say okay, I'm looking at complications after a hip replacement. I'm not going to count a knee fracture that happened after a hip replacement, if that patient happens to have had a hip replacement and a knee replacement at the same time. Next, please.

So, to summarize, ICD-10, although it's created some headaches for us to (indiscernible) then to create categories, it really helps us to investigate more specific device-related questions. It gives us a lot more flexibility in terms of how to design a study. It reduces -- helps us to reduce misclassification, both of the procedure and of the outcome. And it helps reduce selection bias, because we don't really need to exclude anybody just because we can't tell which one it is, or we can't tell which outcome -- if the outcome, we can't clearly identify.

That's my presentation today. Thank you, and happy to take questions later.

DR. MARINAC-DABIC: Thank you, Dr. Mao.

Now we're going to move to presenters dual. Dr. Hongying Jiang and also Dr. Per-

Henrik Randsborg. Hongying Jiang is from CDRH. We already introduced her, from the Office of Orthopedic Devices. And Dr. Randsborg is orthopedic surgeon from Akershus University Hospital in Norway. He also served as the (indiscernible) fellow at Weill Cornell Medicine. And we were fortunate to have him join the collaborative team. They will co-present results of a study that compared the revision rates in total ankle replacement versus ankle arthrodesis in claims data.

Welcome.

DR. JIANG: Hi, everyone. It's Hongying Helen Jiang again. Today, with Dr. Randsborg, we would like to present our recent study on comparing revision rates in ankle replacements versus ankle arthrodesis, fusion, using claims data on behalf of our team, Drs. Jialin Mao, Vincent Devlin, Danica Marinac-Dabic, CAPT Raquel Peat and Art Sedrakyan. Next, please.

First, I would like to present some background and matters. Then Dr. Randsborg will present key results, conclusions, and discussions. As you know, osteoarthritis of the ankle can cause severe reduced quality of life. And ankle arthrodesis (AA), or aka the fusion of the joint has been the main surgical treatment. Total ankle replacements (TAR) were introduced in the 1970s. Although some early TAR designs had high complication and revision rates, the use of TAR has been increasing in the United States.

So, let's compare some key pros and cons of those two procedures, fusion on the left column, and TAR on the right column. The key benefit of fusion is that it removes pain by removing the joint and thus reduced joint movement. In contrast, TAR maintains joint movement, so improves working manner, and protects adjacent joints, and normally have a shorter recovery time.

The disadvantages of fusion include possible limping, secondary pain from adjacent joints, and taking longer time to recover. The key problem with TAR is that some TARs have

higher complication and revision rates. For example, revision rates could be as high as 15% within 5 years post implantation, per the literature. Based on our recent work on STAR ankle safety signal, we were wondering if there's any trend differences in longitudinal claims data between TAR versus fusion, or between mobile bearing and the fixed-bearing TARs, or between cemented versus uncemented TARs. Those are our research questions. Next, please.

There are two well-known claims databases with our collaborator at Cornell Medical School. One is New York State Department of Health Statewide Planning and Research Cooperative System (SPARCS), a comprehensive all-payers data reporting system established in 1979. The other one is California Office of Statewide Health Planning and Development. Both databases have collected patient-level data, including patient demographics, diagnosis and procedures for all hospital inpatient, emergency department and outpatient surgical visits. Next, please.

This is the flow chart to show how we selected our patient population. Basically, we started from all patients who have done either fusion or TAR procedure within the database time frame. From New York State's SPARC System, we have retrieved 1,921 patients. And from California's database, we found 2,170 patients, so a total of a little over 4,000 patients at first.

Then we wanted to ensure the patient populations are comparable, therefore we excluded patients who were younger than 22 years old at the time of the procedure to be consistent with the on-label use of the STAR ankle. We then restricted study inclusion to New York State and California residents, to minimize the possibility that patients received revisions outside of those two states. Then we also excluded patients who were billed for both TAR and AA during the index procedure, because we would not be able to distinguish or compare them. As such, we have a total of 2,945 patients for the crude analysis first.

Next, please.

Please note, the indications for use are not the same for TAR and fusion procedures. For example, fusion has wider indications, and patient characteristics are also different. We therefore conducted a propensity score matched analysis, matching patients with the same indication as for TAR-intended population. This give us 753 patients who could be eligible for both treatments.

These two graphs show the distribution of the two procedures. Solid line is for TAR, and dotted line is for the fusion. Left graph is the distribution before the propensity score matching, and right graph is after matching, where you can see the propensity density were almost overlapped or similar between the two groups, except for age. Age was controlled for in later analysis.

Dr. Randsborg, would you please present our results next? Thank you.

DR. RANDSBORG: Hi. This is Per-Henrik Randsborg, from Oslo, Norway. Thank you very much for letting me co-present this study.

So, what did we find? The total ankle replacements and ankle fusions do not have identical indications. Fusion has a wider indication, such as infection, neuropathic disorders, severe deformities, therefore there are some differences in the patient characteristics. As you see from this table, the total ankle replacement patients were older, were more often white, had less comorbidities, and better healthcare insurance than patients receiving ankle fusion.

Without adjusting for any of these differences in the patient characteristics, total ankle replacements patients had a significant lower risk of revision within two years, quite a large difference of 5.4% versus 9.1, despite the fact that the total ankle replacement patients were older. But remember, the fusion group were sicker, had more morbidities. However, when we did adjust for the differences in baseline characteristics and indications,

with the propensity score matching, we found no statistically significant difference in 2-year revision rate, although the total ankle replacement group still had a lower risk of 5.6% versus 7.6%, but this was not statistically significant.

We found that older age gave lower risk after total ankle replacement, but age did not affect revision risk after ankle fusion. Similarly, gender affected revision rates for fusion, but did not affect revision risk after total ankle replacement. So maybe women had lower risk of nonunion or screw breakage due to a lower weight. A crude analysis of cemented and uncemented total ankle replacements showed no difference in 2-year revision rates. Even sensitivity analysis did not demonstrate any significant differences.

Total ankle replacements have traditionally been offered to older patients with low functional demands, but some new studies indicate that also younger patients benefit from total ankle replacement, and total ankle replacement is also possible in patients with foot deformities, which normally has been considered a contraindication. So, there's an expanding indication, and patients' expectations of a mobile ankle also contributed to the increased use of total ankle replacements.

Fusion have been used in younger and active patients, but also in patients with major comorbidities, possibly due to a fear of severe complications after total ankle replacement. However, it is unclear if frail patients with comorbidities have a less chance of severe complications after fusion than after total ankle replacement. After all, a fusion is also a big operation with potential detrimental complications, including amputations.

In conclusion, we could not demonstrate a statistically significant difference in 2-year revision rates between total ankle replacement and ankle fusion in a propensity score match analysis of similar patients. Younger age is associated with higher revision risk after total ankle replacement, and men have higher revision risk after fusion than women. Cemented or uncemented total ankle replacement designs have similar revision rates.

Lastly, our study showed that total ankle replacement has now caught up with fusion as a surgical treatment for ankle osteoarthritis in New York and California.

Previous studies have shown that fusion was up to six times more used than total ankle replacement, so this is a substantial shift in clinical practice. Thank you very much.

DR. JIANG: Thank you for your attention. This ends my presentation.

DR. MARINAC-DABIC: Thank you very much, Dr. Randsborg and Dr. Jiang.

Now, the last but not least speaker in this session is Flora Sandra Siami. She's a Senior Vice President at the NEST Corning Center, at the Medical Device Innovation Consortium. What you are going to hear today from Ms. Siami is an overview of the National Evaluation System for Health Technology and specific use case on orthopedic data linkage project.

MS. SIAMI: Thank you, CAPT Peat, Danica, and Art, for the invitation to present our NEST efforts. As Danica mentioned, my name is Sandy Siami. I am the Senior Vice President at the Medical Device Innovation Consortium, and I head NEST, National Evaluation System for Health Technology. You've already heard about a few of our test cases already, so you've heard NEST mentioned. I'll talk specifically about one of our test cases on orthopedic linkages.

So, we're on the correct slide, so before jumping in, here's a little bit of background on NEST. NEST has three core initiatives and participates in other programs that facilitate the use of real-world evidence in medical devices. Our first major initiative is our research program. This is where we are building and testing the use of real-world data, not only in regulatory decision making but also for coverage, reimbursement, technology assessment and clinical decision making and such.

We are building a centralized and scalable system for interoperability and providing those real-world evidence standards for things like research methods and data quality,

really answering the question of how real-world evidence can be used throughout the total product life cycle, starting from first in clinical use to the sunsetting of a device, with evidence that really is fit for purpose, right.

Our next initiative is building a first of its kind active surveillance system for medical devices, in order to detect and identify potential safety signals as well as signal refinement, but also provide that active surveillance of both known and emerging signals. This is a cloud-based system. It's intended to be used not only by the FDA but other stakeholders as well, such as industry.

And then finally, our last major initiative is that in 2019, NEST was the first collaborative community to be recognized by the FDA, bringing together diverse stakeholders to identify common needs and provide pathways for solutions. So, NEST really is a community. And this community, as I found out, is really passionate and engaged. Our first project within the collaborative community is focused on unique device identifiers, or UDI, and UDI adoption, specifically in electronic health records to be able to identify devices and link data for real-world evidence research purposes.

Now, I'll take this opportunity to just quick plug. We have a collaborative community think tank on device identification and UDI on November 18th from 11 to 3. I hope you can join.

Certainly, we have other initiatives with NEST, that NEST is involved in, including SHIELD, which is an FDA partnership for Systemic Harmonization and Interoperability of Lab Data, HEPV which focuses on real-world evidence usage for health economics and patient value, kind of building a framework for external evidence methods, and then finally working with our clinical science and medical officer group at MDIC to generate guiding principles for real-world evidence. We also, as you have heard, participate in several MDEpiNet programs to help facilitate the use of registries and coordinated registry networks, such as

Ortho CRN. Next slide, please.

In order to inform the building of our national system, NEST had an open call, and selected 21 test cases, or pilots, to explore that feasibility using various types of real-world data from our network collaborators. Using these test cases, we wanted to identify areas where NEST specifically could play a role in not only creating efficiencies, for example, in contracting or getting use agreements, but also those efficiencies that hover around data governance, curation, aggregation and linkage, device identification and UDI, as well as providing the analytical platform. Next slide.

As you can see here, we have four of our test cases that are concentrating in the orthopedic indications. They range from the intervertebral body fusion devices, OPCs for hip and knee replacement, annular closure devices, and then linking registry data to claims data for total joint and knee arthroplasty. You heard about a couple of these referenced in Session 1 as well as Session 2. And I'll be presenting part of this last test case today. Next slide.

Excuse me. To give a little more of an overview of this test case, this was a retrospective observational cohort study. The purpose was to test the feasibility of linking registry data and claims data. The study was split into two parts. First was working with HealthCore, using the Anthem claims linkage to the American Joint Replacement Registry, or AJRR. The next was Mayo Clinic, using OCTO Labs claim environment, and linking that to AJRR. And I'll be presenting the experience of HealthCore as the test case with Mayo is not yet available. So, next slide.

The aims of the study were twofold, first to conduct anonymous data linkages of registry data to the private claims databases, and then next was to evaluate the clinical outcomes, such as TKA implant survivorship, mortality, revision and reoperation rates, readmission rates, emergency department visits following TKA. And we looked at --

because of some of the delays in this test case, our time span moved, we looked at the time period between 2012 and 2020 for relevant health plan members.

It also looked at a baseline period, 6 months prior to the TKA index date, as well as 90 days follow-up after TKA discharge. And so, the study builds on a model from AJRR, which provides all device manufacturers across access to their device data, that is deidentified. HealthCore had longitudinal data from Anthem, and administrative claims on about 370,000 TKA patients. HealthCore then utilized DataVance privacy preserving software to aggregate and link tokenized data in order to conduct anonymous data linkage, excuse me, between members and the AJRR registry and members and the Anthem administrative claims data.

And then before going any further, I want to really thank HealthCore and Kevin Haynes, who was the principal investigator of this part of the study, who did the work. I'm going to present processes, successes and challenges, but however because the results of this test case have not yet been made public, I won't be presenting scientific results, but maybe you'll sit on the edge of your seat and look for scientific results in those presentations soon. Next slide.

So HealthCore used its HealthCore Integrated Research Database, or HIRD, and this contains Anthem administrative claims data, and really created a computable phenotype using CPT as well as ICD-9 and ICD-10 procedure codes to identify the population with TKA. What's important to note, though, as they were going through the exercise, they realized the ICD-9 codes didn't provide the indication of whether or not this was a right or left knee that was being worked on. So, ICD-10 did end up being used for purposes of the study.

Using that data, HealthCore then compared the AJRR cases versus the Anthem claims population in identifying survivorship. We looked at -- they looked at 90-day revisions and reoperates, 90-day readmission rates, and just for the claims data because it wasn't

available in the AJRR set, 90-day emergency department visits. Next slide.

In executing this test case, certainly we had success, we had challenges. A few of the successes included the successful implementation of the computable phenotypes that were developed in the claims environment, using the CPT and ICD-10 codes as well as the successful characterization of utilization of both the CPT and ICD-10 to identify those cohorts of interest. The team was also able to successfully identify and characterize outcomes for this population according to the protocol specifications.

As you can imagine, some of the challenges, one of the biggest was the data sharing agreement between HealthCore and the American Academy of Orthopedic Surgeons (AAOS), who owns the AJRR registry. And then also, because this test case was executed knee deep right in the, you know, beginning of the pandemic, it really impacted resourcing. HealthCore especially had to pivot and concentrate on COVID-19 activities, for example. So, there were some delays here.

But clearly, the study has implications for further anonymous data linkages to support FDA-regulated activities in active medical device surveillance using claims as a supplement to registry data. Next slide.

So, to conclude, this test case really showcases how health plans can be used to supplement registry data. The results, which I didn't present today, really provided that descriptive characterization of TKA for the overlap of members, both in the registry and in the claims environment, again from the period 2012 to 2020. And the registry data provided the etiology for TKA failure, and the claims data provided a more robust environment to determine again, the survivorship, the 90-day revision reoperates, the 90-day readmission rates and the ER visits following TKA.

And then finally, next slide, I want to acknowledge that our funding source for this activity presented today was through a grant by the FDA. Thank you very much.

DR. MARINAC-DABIC: Thank you very much for excellent talk.

We would like now to start the moderated discussion, so I invite back our moderators to actually facilitate the group discussion on patient-centered outcomes.

Dr. Sedrakyan?

DR. SEDRAKYAN: Good afternoon.

DR. MARINAC-DABIC: And Dr. Devlin.

DR. DEVLIN: I'll start off with a question then for Dr. Forsberg. I enjoyed your talk. It's really innovative how you're approaching this area. One principle that we hold high is simplicity. In thinking about your data on upper and lower extremity amputees, do you think that we'll end up needing two different sets of PROMs, one for upper and one for lower extremity? Or do you think that we'll be able to end up at the end of your work with a single PROM that could be generalized to both anatomic areas?

CAPT FORSBERG: That's an excellent question, Dr. Devlin. Thank you very much for asking. We're in the process of writing a reliability and validity paper, and I can -- and it seems as though we can use existing patient-reported outcomes to achieve what we're after, better function, less pain, greater patient satisfaction. So, it's a pretty heavy lift to design a patient-reported outcome measure in these unique patient populations, because there just aren't a lot of transhumeral amputees who are willing to undergo this procedure.

So, short answer is, we're going to go with what we have for now, and I think that's going to carry the day, but I reserve the right to revise that opinion after this paper comes out.

DR. DEVLIN: Thank you very much. That -- we'll look forward to it.

DR. SEDRAKYAN: Maybe I can ask him this question. I really like the progress that NEST made with this pilot project, Sandy. I think it's a really good chance for us to capitalize on it and develop a stronger collaboration, and in terms of projects that we do within

MDEpiNet and integrate better with NEST, and NEST's activities. What's your thinking about the pathway and -- in orthopedics? What's your vision how this can build stronger NEST presence through the use of Ortho CRN?

MS. SIAMI: Thanks Art, for the question. I think the value of NEST and how it can incorporate in not just Ortho CRN, but other registries will become apparent once we have our system. Right now, as you can imagine, there isn't an integrated system that can use different sources of data very easily, right. And that's kind of the beauty of NEST bringing in all of the different sources of data to provide a robust environment.

And so, I do see that we will be integrating more within registries, and supplementing registry data not just with claims data but electronic health records and patient-generated data. But we have to solve some basic problems, which we are working on through our committees, and working groups, and as I said, you know, NEST is a community, and their passion is really palpable. And I'm confident that we'll be seeing that, actually, in the next few months.

DR. SEDRAKYAN: Oh, that's great. I just, I feel like this is a really good chance, sometimes, in early maybe 2022, once like some of the processes you're going through in terms of MDUFA and other aspects. But, you know, you learned a lot about HIVE today as well, as an integrator platform. And it's sort of an independent FDA-maintained platform that I hope NEST will consider bringing not only EHRs data but also collaborative systems within MDEpiNet, like the CRNs that have been building.

And also, the apps that NEST certainly funded are important to continue incorporating into the fabric of NEST, right, bringing patient-reported outcomes more into the same environment, with really these exciting tools. I'm just thinking, like the timing. It is really fantastic.

In terms of non-Medicare data and integrating those, maybe I can ask question to

Jialin Mao. Can you, Jialin, maybe comment about difficulties with non-Medicare data to link with the registry, successes we have, but also challenges, like with partners like HealthCore and also other private groups that are bringing this claims data together?

The reason I want Jialin to comment about this is because we often, in HealthCore, recently we had this experience to create really longitudinal files. It's very challenging. It starts sort of falling apart at 5-year follow-up. A very small group of patients have that continuity of a longer-term follow-up. But I'm going to ask Jialin to comment more about experience with New York and California in linkages with the registries, and also other challenges.

DR. MAO: Yeah. I think, well I can first speak about some success and make everybody happier. So, the successes that we -- although that we had a very good linkage with Medicare, and visions of Medicare (indiscernible). So, the success that we -- when we extended this to do the linkage with state claims data, it actually gives us a more complete sample, because as we all know, Medicare now has Medicare Advantage versus Medicare B plus service. And Medicare Advantage patients are not A and B plus service data.

And that being said, although the linkage rate is really good, you apply a condition of probability of a patient being a Medicare Advantage -- being not Medicare Advantage patient, and the overall numbers just drop down. And when we did it with state data, that becomes less of a problem, because everybody is in there, regardless of their insurance. I would say that is a success. So, we basically retained the original success rate. For example, our algorithm was able to link over 90% of patients. And because of Medicare Advantage, it dropped down to like 190 -- it dropped down to 100 people in -- 80 people in 100 people. But then, when it goes to the state, 100 people, we can still keep the 90 patients that were linked, regardless of what insurance they have.

But then there are a few difficulties when it comes to non-Medicare, for instance. If

we know that if they have Medicare, and Medicare tracks everybody through statistics, and everything would be there. And we can use that to very reliably look at mortality, for example, in the (indiscernible). But then once we go outside Medicare, and we go to the state, and even now we are working with the states to get vital statistics data. And then it just, if the patient leaves the state, then we lose their medical statistics.

Same thing applies to work with HealthCore or other private care, a private insurance company is that it's enrollment contingent. So, once they leave the insurance, once they change jobs, they move to other places, then we lose them. And that becomes an issue when you're really looking at very long-term outcomes, beyond the first 2 or 3 years, if you want to keep the continuity. Am I missing anything?

DR. SEDRAKYAN: How long did it take for you to get the vital statistics process going with the New York State that allows to get mortality data in addition to just longitudinal follow-up on patients' admissions and discharges?

DR. MAO: That's taking me 2 years now, and still ongoing. I think the state SPARCS people vital statistics people did not honor me because I dislike them so much. But yeah, hopefully we'll get there soon.

DR. SEDRAKYAN: Well, this -- I wanted to highlight this for our partners, because the infrastructure investments we've been making is for the future. This is not something that is easy to replicate, do from ground up. I think -- and collaboration with Kaiser is also critical, because Kaiser has been a wonderful partner and covers significant portion of U.S. population in a closed-circuit system for follow-up. So, I think we should try more to take advantage of this data that we've been building and updating annually for a lot of orthopedics research in the future and linkages with various registries.

DR. MARINAC-DABIC: Art and Vince, we are -- we have probably a couple more minutes and then we need to wrap up, because it's 10 minutes behind. Any --

DR. SEDRAKYAN: Sure. Sure.

DR. MARINAC-DABIC: Any other thoughts?

DR. DEVLIN: Sure. I just had a quick question for Dr. Jiang and Dr. Randsborg, whoever would like to answer. You know, excellent study, and I can see that there'll be future work in this area. Do you have any plans to incorporate specific device types into your research? And if so, what challenges and hurdles do you expect in linking the registries to obtain more device-specific data?

DR. RANDSBORG: Thank you very much for that question. Helen, I think you should maybe comment on your, on the current project with fixed and mobile bearing designs. I think that's a continuation of this project.

DR. JIANG: Yeah. We have different projects, you know, being planned. Another similar project is how to compare the revision rates based on other real-world evidence data such as the MDR data that I did receive, not necessarily, Dr. Devlin, like you suggested. Though we've been looking at some MDR data that we have, and try to compare, you know, different TARs, and look at their revision rates and reasons for revisions, you know, to further kind of find out the, kind of the potential reasons for those revisions, if it's truly related to the material, polyethylene material or could be other some design issues for different types of devices.

However, there are limitations to the MDR data, as most of us know. So, I think, you know, expanding that to other data sources, like other, you know, registry or claims data will be very helpful. And with longer-time data, that will be very useful as well.

DR. DEVLIN: Well great. Well thank you. Thank you so much for that great answer. And at this point, in view of the time we'll have to wrap up and turn things back over to Dr. Marinac-Dabic.

DR. MARINAC-DABIC: Thank you very much.

I would like to thank all the panelists and speakers and moderators and everyone who actually made this second session a great success. We will probably take 5-minute break instead of 10-minute break, just to allow for the transition. And then we'll be back for the last session of the day. Thank you.

(Off the record at 2:14 p.m.)

(Onn the record at 2:20 p.m.)

DR. MARINAC-DABIC: Those of you who are joining us, rejoining us again, to the third and the last session of Orthopedic CRN Annual Conference today. For those of you who, you don't have a chance to join us until now, we had two productive sessions. The last one just ended up. We had seven speakers, discussions focusing on mobile apps and also patient-centered outcomes, with a lot of fruitful discussions and directions for the future.

Now it's my great pleasure to actually kick start the, our last session, which is going to be focusing on national and international collaborations. And as the first speaker, it's my honor to introduce Professor Robert Nelissen, who is the professor of orthopedics and the Chairman of the Department of Orthopaedics at the Leiden University Medical Center. He will present an overview of international efforts, prioritizing the questions for USA and EU collaborations.

And before Professor Nelissen begins, I also would like to introduce my co-moderator for this session, and that's Dr. Liz Paxton, who I already introduced earlier. And I think we're in good shape to start this last session.

DR. NELISSEN: Okay. Well, thank you, Danica. I think I sent the PowerPoint to you, so I think somebody is now asked to push the button, okay, or can I share the screen? What's the easiest? That's something I didn't figure out.

DR. MARINAC-DABIC: If you can just say, next slide, and someone will --

DR. NELISSEN: Oh, okay. Perfect. Yes. Yeah. So, first slide, please. Oh wait, I have

to screen, I think. All have been sent.

DR. MARINAC-DABIC: Shall we go back a slide? Do you see your slides?

DR. NELISSEN: No, no. I've seen it -- I only see you.

DR. MARINAC-DABIC: Okay. So -- okay. The studio, maybe can help?

DR. NELISSEN: I could organize perhaps something that I --

DR. MARINAC-DABIC: If you click on a view, or FDA camera, what can you see?

DR. NELISSEN: I only have my iPad now here. Let's see, it's -- usually it's working. I could do something else. Wait a second. Is this happening again? You see something? Nothing. I'll try something else. And I will be in control. That's easier. Well, that's forbidden, because I'm in the hospital.

DR. MARINAC-DABIC: If you have your slide deck --

DR. NELISSEN: Yeah.

DR. MARINAC-DABIC: -- in your computer, you can actually just tell us next slide, and we'll advance our version, because we can see the slide. You can't.

DR. NELISSEN: Oh, okay. Oh, I think that's easier. I think what I'll do is just -- sorry for this.

DR. MARINAC-DABIC: Let's go back to this, let's go back to the slide that's --

DR. NELISSEN: Well, yeah. You know what I'll do? I just thought of it. If you can see the slides right now, that's fine. I have them in front of me.

So, thank you for the invitation. My purpose is to take you along a little on the international collaboration within the orthopedics, U.S., E.U. -- or Europe, I think. Next slide.

You'll see -- if that's fine. You see a slide with CORE-MD, that's a recent Horizon 2020 grant which has been granted to us in the cardiovascular fields. Alan Fraser and myself are in the lead for this big grant. We just started, April 1st. And the background is,

is that we want to have coordinating research in evidence for medical devices, and especially for regulators. We know there's a lot of confusion by the regulators on what kind evidence they can use. So, our aim is to solve this problem within 3 years. It's only a small grant, 2.5 million euros. Anyway. Next slide.

You see some of my disclosures. I'm rather active, worldwide. I recently became the chairman for the (indiscernible) for Orthopaedics Trauma and Rehabilitation. That's new medical device regulations. My committee has sent for members, and we are going to evaluate new and novel devices.

Well then, to the topic. You see a slide now with different implants, I hope. Okay, great. So, in the past, a lot of effort has been put into hips and knees, but -- next slides -- you see that's -- in my talk I want to focus more on the tsunami of shoulder implants. At least in Netherlands, there's a 50% increase of reverse shoulder implant. The same is true for the U.K. and Wales. And the interesting thing is also there's a, I think a tsunami outside Europe, but especially some in Europe, and also in the U.S., on those disc implants, which are not used in Netherlands since 50 years. The advice of the Orthopedic Association was not to use these devices because the results were very bad. So, I think that's the challenge for us. Next slide.

You see the European map. And in E.U., we have about 450 million people, Europe, including U.K. and Wales, well that just left us, but they're still part of Europe, 750 million citizens, so it's a huge number of citizens. And you can see that also a lot of those major registries are around in Europe. The Swedes are the oldest, but the biggest is the U.K. and Wales, the biggest worldwide. And the second biggest is the Netherlands. We have now more than 900,000 implants in. And when you count these numbers up, you're talking about 7 million implants in the -- only in the European space, which can be used for validation of their success and their efficacy. Next slide.

In the old days, well even currently we still evaluate these implants, hips and knees especially, on why they loosen. And that's considered to being a revision. When the implant's painful, you revise it, and revision rates, or the survival rates is the way, how we evaluate these implants, in general, in registries. And we also use PROMs, which are done by the majority of all registries. I think the interesting thing is -- next slide.

You see, in this slide, the revision rate of about 350,000 hips, which are being done in the Netherlands. Well, if you follow up, you can see, if you follow up, the average all (indiscernible) patients will have a revision rate at 12 years of 4-1/2%. Next slide. And next slide.

But when you look at the 8-year revision rate, you see that that rate is about 3.6%. Why is it important? Next slide.

Hopefully now you see the shoulder implants, I think. While shoulder implants are not that often done in the Netherlands, nor in the U.K., as total hips and total knees -- we perform about 40,000 hips a year in the Netherlands, in the U.K., I think, around 100,000, but you see there's a huge difference in the revision rates at 6 to 8 years. Next slide.

Which is about four times higher as compared to total hip and total knee. So, I think there's a challenge for us, and also the orthopedic but also regulator community, how to address this. Next slide.

I can't see my slides, but I think now you see the slides of the increase of hips and knee implants, and shoulder implants. You see also the downward slope in 2020 due to COVID. That had a huge impact on the prime rate, total hip and total knee, and shoulder implants in Netherlands. Not for (indiscernible) implants, but for these primary implants. Next slide.

You see, in the Netherlands, there was only a very little increase in the last 5 years, around 50 to 70% for hips and knees. So, the predictions which were done 50 years ago, by

Kurtz are not there anymore. But what you do see, however, is that for shoulder implants, there's a huge increase, about 32%. And for spine implants, even in Netherlands, also in the U.K. and Wales, and different parts in Europe, there are very little data around. In the Netherlands, the spine, which we stopped two years ago, due to a lack of funding, so there's a challenge, because a lot of these things are being done. Next slide.

It's a paper from a group from Wu, et al, recent paper. You see, worldwide the global increase of lower back problems. And you see, in the eastern part of Europe, and the western part, you see this increase also of this population, between the age of 45, 50 years, is the highest incidence. So, there is potentially a need to do something. It may be conservative, but also, surgery. Next slide.

But when you look at these implants, these disc implant as well as shoulder implants, again the same metrics can be used as for the hips and knees. They need to be fixed in there, in the joints, to the bone. However, with these implants -- next slide -- the PROMs measures are much more important because PROMs are probably very much related. Next slide.

Here you see the brain, with the PROM score. The indication is very important for those shoulder joints as well as spinal implants, is of course they have to be fixed in the bone. But the PROM score is even more important, and that's a challenge. How should we evaluate this? Next slide.

There's a push, a thing from the market. That slide I got from the internet by iData Research. And -- next slide -- you see, the industry that projects a lot of cemented spinal surgery. Next slide.

You can see this implants, plates and screws for this, cervical spine, lower back spine, but also these artificial discs. And the big question still is, do they improve? Next slide.

Interesting paper. It's probably all known to you, from the JAMA. You see, when implants are evaluated, cardiovascular, orthopedic, and when it's done too fast -- next slide -- you see -- next slide -- that's the revision rate, and the withdrawal from the market, the recall is three times higher. So, in general, you can state, that's -- when there's (indiscernible) speed for approval, there's also -- over strong evidence, clinical evidence, as is said in the new medical device regulations, then there is a big tsunami of revision and safety issues with patient care.

Well, my point is, we should collaborate, especially for those implants, shoulders, spinal implants, where the numbers are lower than for hips and knees. And it could be a nice opportunity between the E.U., I think, but I would like it, put it broader, Europe and the U.S., and of course also Australia, to go further.

Well, in recent past -- next slide -- Art Sedrakyan start with his ICOR consortium, and they produced a lot of papers, between the U.S., Australia, the Scandinavians, mainly, and also some in the, within elements, but that was mainly focused on hips and knees. Next slide.

And the interesting thing is, when you look at the PROM score for hips -- next slide -- for shoulders, it's a very interesting thing. So, for hips, as well as for knees, you see a nice increase in quality-of-life scores, but the interesting thing, for shoulder, it's not that evident. That's very interesting. So, we need something else. We need to collaborate, to put us forward to the next level. We have some experience. These are some papers from NORE. Next slide.

Some interesting paper within ISAR, that's Australia, Europe and the U.S., Kaiser-Permanente, we work together. Next slide. A recent paper we published within the Netherlands' database, which is far bigger than the whole NORE group. But it's very interesting to compare NORE data from Scandinavia with the Netherlands. That's the way

forward, international collaboration, also within the European space. Next slide.

We have some experience from ICOR, and also with Art Sedrakyan, on the appraisal of new implants. Next slide.

I think, hopefully now you see the score and the thing. That's coordinated research in evidence for medical devices. We have about 23 groups, from Oxford, Karolinska, from (indiscernible), from Leiden University, from Ana Ruthia (ph.), from Vienna, the HTA scientists. And what we actually aim for is evaluate existing methods, like just the survival analysis, competing risks, randomized controlled trials, A.I., but also, what's the validity of registries? Because a lot of regulators in Europe, and it's probably same thing in the U.S., are in doubt how to use these registry data. What is completeness? Should it be 100% confidence, et cetera?

At least we try to solve this problem, but it should be done in conjunction with you. That's the reason we have two, well three people from the U.S. onboard. Bob Bisko (ph.) is E.U. scientific officer, but Art Sedrakyan is one of the member of advisory board. Rita Hindburg (ph.), she's from the Red Brook (ph.), from San Francisco. She's part of the advisory board. So, I think it's nice to have this collaboration, on a global level. Next slide.

It's not about these implants, cardiovascular, hips, knees, whatever you call it. it's more about patients, in the end. It's about how can you put safety forward to these patients. The answer is, we need a ICOR 2.0 in collaboration with our new consortium, CORE-MD, in Europe. I think that's now open for discussion, and for you to look at the website, of course. Thank you.

DR. MARINAC-DABIC: Thank you very much, Dr. Nelissen. That was great presentation, despite some slight discrepancy in the order of the slides. We'll double check that later with the studio, and maybe we'll ask you to resend your version again, make sure. But it was very informative, and I thank you for that on behalf of everybody here.

So now, let's move to the next speaker, and that would be actually joint presentation. I believe Dr. Art Sedrakyan is going to give the talk, but I know that he and Dr. Paxton collaborated on the presentation about distributed analyses of the national and international data to enable new collaborations.

DR. SEDRAKYAN: Thank you, Danica.

I just wanted to recognize, I think Rob pointed out, but history of ICOR, I'd like to recognize both Danica and Liz being really important co-leads of the ICOR initiatives, and they are really critical for making it a success. And this presentation I'm giving on behalf of our team, in collaboration with Dr. Paxton because Kaiser Permanente and ISAR registries that she leads are extremely important and critical for success of ICOR and future international collaborations, including really collaborating with CORE-MD that Rob highlighted, because all of these partners are part of the same family, same -- they go to the same meetings. So, it's really important for us to be on the same page of what we'd like to achieve in the future. Next slide, please.

I just wanted to highlight a little bit, but I mean, you heard about MDEpiNet, just highlighting that our organization is dedicated to advancing the science of medical device epidemiology and outcomes research in collaboration with NEST. We'd like to help set up also NEST mobile infrastructure, using our coordinated registry networks. Next slide.

Coordinated registry networks are really critical. When there is a registry, or there is opportunity to build a registry, and leverage all the claims data source, there's EHRs and patient-reported, and patient-generated data that we heard today, it's a mechanism for us to try to take advantage of all these wonderful real-world data sources in a concerted and organized fashion, activate particular tiled linkages when they're possible, physical, and necessary. And really essentially, this is wonderful mechanism to do research, surveillance, and just quality improvement overall. Next slide.

At MDEpiNet Coordinating Center, we have been building this data capacity, in terms of accumulating a lot of claims data, partnering with registries such as Kaiser Permanente, partnering with like Vascular Quality Initiative, or National Hernia Registry. We try to take advantage of also data sources from states, and if there are chart collaborators, such as a collaborative EHR network in New York State, where many hospitals participate, we also incorporate that sort of a data into the CRN mechanism. And we have some pilot successes to share about that as well. Next.

Danica will be talking about ICOR achievements. It really was said so many times, we're tired of saying it, but clearly, we need ICOR 2.0 that Rob highlighted. The past is important, but it's also important to consider if possible, to energize the community and launch new studies in the future. Next.

What we have done in the past within ICOR, and it was really unique, to enable these collaborations back 7, 8 years ago, was first time ever a mechanism of distributed data analysis. A Kaiser statistician, in collaboration with Cornell's statistician came up with this fantastic way of creating a mechanism for centrally sharing codes, harmonized coding, and training each partner to run these codes on their datasets, which wasn't a simple task.

We thought it's going to be very straightforward, but it took a lot of time, a lot of face-to-face meetings before folks were comfortable and were able to run this analysis, and then provide a summary information back on survivorship of joint implants, that we then used to combine them in a pragmatic fashion and come up with a survival analysis using data from many, many partners. Sometimes we have six partners. In other instances, might have four national partners, but this was unique, and it was never even done in a pharmaceutical research setting before.

The collaborations, internationally, are plenty. There are so many collaborations going on. A hospital entering data into a data centralized repository for clinical trial is also

international collaboration. But what didn't happen before when a national data, from different countries, run in form of registries would be coming together to address a global question. So that's a unique aspect of this system that is definitely different from anything we've done in the past. So, we really -- next slide.

We would like to advance this methodology, and while we used it 7, 8 years ago, would like to also take advantage of some modern developments, including some of our partner groups recently introduced a new kind of models that we're incorporating, so we can use Bayesian methods and also nonlinear models that will help us handle some of the inefficiencies that we've seen when we pulled data, and some of the cell numbers, when we had to pull were really small, and it created some challenges. Also, a lot of zeros created challenges.

So, we came up with much more advanced methodology now, and I hope it can be used more in future, in collaboration with CORE-MD and ISAR group that Liz is coordinating internationally. Next.

So, I just want to highlight a few studies more recently that International Consortium of Vascular Registries did, a partner organization that learned a lot from ICOR, in a vascular setting. There wasn't any international work of similar kind, that orthopedic surgeons led. So, we helped the community, Vascunet, which is a European organization that was establishing some collaborations, link up with our own U.S. national registry, called VQI. And VQI has been really a leader in providing this registry information and doing quality improvement nationally, and collaborating with FDA, with the Division, OCEA that is led by Dr. Caños, who will be also joining today at the end to share his thoughts. And -- next slide.

So, I talked about CRN, but essentially through data linkages, now in the United States we're able to establish this low-cost and effective way to provide longitudinal follow-up on patients that were -- whether it's joint replacement or vascular procedures, many

care data linkage that you heard about, cleans data linkage that you heard about from Dr. Mao, and Sandi Siami from NEST. These are really important test cases that we already leverage in building these linked data sources. Next.

And here is an example, when we not only collaborated with a registry, but also helped them to enrich their data with the data linkage. In Australia, a national vascular registry is, it established collaboration with our MDF in a chapter, in Sydney, in University of New South Wales -- next slide -- and essentially replicated the model that we have established in the United States with the vascular registry, VISION. They linked their national registry with the same methodology of deterministic and probabilistic matching to the various vital statistics data in the state of New South Wales.

And New South Wales is a very large state covering over 30% population of Australia, so it becomes a wonderful resource, because you immediately have 1/3 of the country covered, in terms of linkage for long-term follow-up. Next slide.

So, I can skip the results. It's really about specific technology evaluation. Next one.

So, what we essentially can achieve now, we've been -- and this is a vascular example, but by helping our partner groups in different countries to do data linkages, or leverage their claims data sources to have more data, and reach their data, and then sort of establish stronger methodology with distributed analysis that I talked about to bring this all together for global studies.

So, I think the future is not just about leveraging already collected data, but also creating this learning network of enriching each other's data, learning from each other how we can get long-term outcomes. And that cements the collaboration in the long term, because there's not only ties to do studies but also ties of how to strengthen the infrastructure. Next.

So, in essence, this collaboration internationally can be taken to the next level. And I

hope we will continue working with our partners globally to achieve that. Next.

One comment, again we talked about HIVE today. I just would like to highlight that this is really helpful to us, a launch. On a local level, if there are partner groups in hospitals, I'd like to take advantage of it to set up local data collection system, local registries, a hospital system-wide registries. Our group can help and leverage the technologies that Vahan Simonyan today talked about. And we hope we can deploy this in a number of institutions nationally to work with collaborative clinical trials as well. Next.

Yeah, the ICBR also help to do clinical studies. Like once these networks are in place, such as the one that Dr. Nelissen is building with the (indiscernible) in Europe, it allows also launching clinical studies and clinical trials leveraging the registries. In this example, the vascular collaborative that I just talked about, ICBR launched very interesting investigation using HIVE platform to study a off-label indication, like in outcomes in ruptured abdominal aortic aneurisms for the technology study used to repair aneurisms. So, this was really now given almost complete now with the help of our data core, run by Jialin Mau that you also heard about today. Next.

That's my final slide. Thank you very much. Pass it back to Danica.

DR. MARINAC-DABIC: Thank you very much.

Now, I am going to introduce myself as the last speaker. And then I'm going to turn it over to my co-moderator, Dr. Paxton, to moderate the discussion.

So -- yes. I am going to try to reflect on the evolution of international collaborations, so touch upon some of the drivers, tools, and models to advance partnerships, build on some of the discussions that Art had already highlighted and just put a little bit more of a different spin on some of them from my FDA perspective. Next slide.

I am focused primarily on the International Consortium of Orthopaedic Registries, as I go over some of these points. Next slide.

For those who remember this paper, and those who didn't look at that, I would like to point it toward the paper that we wrote back in 2001, at the first themed issue of the JBJS journal, featuring the ICOR, as it was launched that same year. In May we had the first meeting. In November, this was published. So, as you can imagine, all the studies that were there, and these lessons learned that we've highlighted in this paper, actually produced in a matter of months, which was, I think unprecedented at the time. Next slide.

So, now when we look back at 2010 and 2011, when the ICOR was a very novel way of integrating all these learnings across the globe, to where advancing the knowledge of orthopedic devices, I'd like to sort of talk about these from the perspective of how we can build on the key accomplishments and the impact. We've heard today, Sandy Siami was talking about the NEST strategic activities and building the national infrastructure, how we can actually incorporate some of this learning today into the evolving initiatives that FDA is spearheading, and NEST is also implementing, then how to fully understand the learnings and the best practices, meaning how we can, in fact, not to relearn the history but rather learn from it and be able to implement it into the novel initiatives, moving forward.

Knowing those two things, now how that can help us to think about and address the questions. What are the key drivers today? What has changed since 2010? What are the novel tools that we have at our disposal today that we didn't have in 2010? What are the models that exist that we can build on?

Now, it's also important to reflect on the trust and the relationships and the champions and the partners that we had at that time, and also to take the stock where we are today. There are some still key players in these initiatives that we can continue to rely on to actually evolve into the next phase of the ICOR if we agree as a community that would be the next step.

And then also it's important to address the question, what are the incentives that we

have today? Some old ones, some new possible ones that we don't even think about, and we think about what we can actually do with those incentives and how we can incentivize these communities. What is the FDA role in some of these incentives as well? And how we can best divide and -- or stimulate national and international cooperation. So, these are the sort of thinking I was hoping that in the discussion that will follow we're going to reflect on as part of our last session. Next slide.

Again, the familiar picture, at the time there were 29 registries. At this first inaugural meeting, there was actually all our registries that we were aware of, across the globe. We sent an invitation to them, and all 29 came to the FDA. So now looking back in some of these pictures, you will see some of the familiar faces, Art Sedrakyan, Rob Nelissen's there, Liz Paxton, and others. And those are all the list of the registries. Some of them were very tiny at the time when we had this meeting, like American Joint Replacement Registry and now it is actually very much grown into the national registry. So again -- next slide.

I wanted to, also to highlight, and what was the mission and the goal at the time. Really, we wanted to advance the research and improve evidence for the safety and effective of orthopedic devices and procedure. This is very relevant, and normal mission end goal even for today. We know much more about these devices, but there's still gaps that we fill.

We wanted to harmonize the data among U.S.-based and international orthopedic registries. At that time, all the data were actually quite in a very individualized way, and there were not that many efforts to make them interoperable or harmonized. We wanted to implement a distributed data analysis system and conduct studies to monitor the safety and effectiveness of orthopedic devices, and just focus first on keeping on studies and then move to other areas. At that time, the first contract was awarded to Cornell-Kaiser team,

which still leads this effort in Ortho CRN research space. Next slide.

So, again learning from the history means that recognizing what were the key accomplishments that ICOR established at the time. One, the first one that I would like to highlight here is the development of the ICOR global standardization database. The idea was really to develop the global standardized specification system of hip and knee implantable devices based on their clinical attributes, and those characteristics that are important to clinical space, so advance the implementation of UDI and the postmarket surveys.

So again, this was -- the vision was to be -- to go beyond the UDI requirements, but to add actually those additional attributes that are important. And previously, keep in mind, at that time each registry developed and maintained their own clinical attributes for that database. There was no standardization at the time. So, with the leadership of Professor Stephen Reyes (ph.) from Australia, and many, many, many registry leaders across the globe, this actually was achieved. Next slide.

The second key accomplishment that Art spoke about is this development of the Distributed Data Network System for remote access in clinical and other data sources in a secured and controlled -- in a way that data continue to be controlled by data owners, again minimizing the data transfer, reducing security, proprietary, legal and privacy concerns, and eliminating a lot of hurdles really, and promoting the national discussion in this space. So, next slide.

So, these are some of the papers that were published in the first, I believe in the first supplement of our journal, JBJS. But then the second one followed 3 years after that, in which we continued to promote these international cooperations. Also, I wanted to say that these efforts very much were inspirational to the U.S. national efforts to start thinking about the national evaluation system for health technology. In June of 2012, FDA held the

first public meeting to actually launch the efforts to develop the national system.

And if you can recall, that was a 4-day meeting, established really some of the key vision statements for us to follow in the (indiscernible) on the establishment of the national system. All the same, June of the same year, FDA held advisory panel meeting on metal-on-metal hips. And again, some of these studies were actually presented during that meeting. And during our talk, the FDA made the decision about metal-on-metal hips with the contributions from across the globe that was present during that meeting. Next slide.

In addition to these key accomplishments, I would like to point towards some of the more lasting accomplishments. They serve as a model to build other international registries, International Consortium of Cardiovascular Registries for example. International Society for Arthroplasty Registries already existed at the time, but ICOR movement very much strengthened the existing registry participation in ISAR, and in fact led to a very, I would say increased number of cooperative studies within ISAR, which we are really very, very proud of, and happy for, to see that progress made.

Then it also informed the International Medical Device Regulators Forum efforts. Many of these orthopedics lessons learned were embedded in the IMDRF Patient Registry documents, three of them, that were published from 2015 to 2017. It also informed the U.S. National Medical Device Registry Task Force. Again, landmark report issued in 2015, which coined the word, coordinated registry network, or strategically coordinated registry network. And you can see a lot of these (indiscernible) to orthopedics helped shape up the future of the national system in the U.S., and as I mentioned, informed the U.S. vision for NEST beyond 2012, and informed Strategically Coordinated Registry Network Initiative, that we are implementing today. Next slide.

Some of the driving forces are obviously known to many on this conference today. Health technology ecosystem today is focusing much more on real-world evidence than it

did in 2010, so that we should actually take advantage of that. There are many patient-centered efforts, an initiative across the federal partners and other non-federal entities. We have many methodological advances. Data science evolved as a driving force, and many digital innovations today that we didn't have then. But we can use them now, to help us raise the question, what is the regulatory rate of real-world evidence in orthopedics? Moving -- going to the next slide. Next slide, please.

So, some of these -- and this is, I think, one of my last slides. I just would like to say, and to sort of build on what Dr. Simonyan presented today, in the context of the HIVE, with the novel tools, machine learning, artificial intelligence, blockchain, why do we talk about data collection and quality control, or data harmonization, and sanitization or data aggregation and storage, or data analytics, or permission-based consenting frameworks, or defining the process for transparency?

We are now in a much better place than we were in 2010 and 2011. So again, these are some of these drivers and opportunities that we should take very seriously as we decide strategically, what is the future of the international cooperations in the orthopedic area? Next slide.

I'm not going to go through this. We already heard about infrastructure. I'll just skip those two slides, in the interest of time. Next slide. Next slide. We heard it twice today.

So, I would like to conclude with some thoughts about what might come next in the orthopedic space, that builds on the discussion that we've heard today from our panelists and speakers. One potential area would be, if you think about the International Consortium of Spinal Registries, both in adult and pediatric space. Also, to think about the International Consortium of Shoulder Registries, and there are many efforts in that space, including some of the leading areas in -- led by our own American Academy of Orthopedic Surgeons. But the idea is really to do it from the collaborative perspective, multi-stakeholder involvement

and fact-caused disciplinary approach, and many more.

Thank you very much for your attention today, and I'll skip some of these slides in the interest of time because we would like to engage now in the panel discussion when we stop this.

DR. PAXTON: Thank you, Danica, Art, and Rob for those excellent presentations. I thought first of all we should start off with a discussion on what are the key drivers for success for ICOR 2.0.

Rob, do you want to get us started, in terms of your thoughts?

(Pause.)

DR. PAXTON: Danica or Art, would you like to comment?

DR. NELISSEN: Can you hear me?

DR. SEDRAKYAN: Oh great.

DR. PAXTON: Oh, are you there?

DR. NELISSEN: Yes. You hear me now?

DR. PAXTON: Very good. Yes.

DR. NELISSEN: Okay. I was just, got cut off. Sorry. I think, yeah, what's -- I think it's always, what's in it for me, but then on a higher (indiscernible) level, I think it's essential to have international cooperation, especially on devices which are less frequently, we use. So, and yeah, how can we -- with things put forward, things just by science? And ICOR has already proven that it can establish this, this international cooperation. And we've just recently established ISAR. We have -- well, the difference with NORE is that it's part of EFORT.

So, I think, for ISAR and -- yeah, and NORE and EFORT, that's -- at least we have the European continent. And in the U.S., you have of course AAOS of course, which work together. So, I think, put it forward on these aspects, where the clinical -- well at least it's

more of a work around. I should note, we only, I think, for researchers and then methodologists, it should come back in a clinical practice. What's -- so, and that's what I (indiscernible) at EFORT, and NORE is only an education committee over EFORT. That's the thing it.

But it brings forward the importance of ISAR. That's the reason, in Lisbon, we have again an ISAR NORE session. And ISAR is global, then more importance. But I think that's the issue. So, I think it's important for regulators, like Danica, or Bisko in Europe, and in Japan, et cetera. But I think like the general expectation of being an orthopedic surgeon, I did surgery today. I think it's important for my practice.

So, make the link to the clinicians, I think. That's -- I think that's at least a background analysis for CORE, I mean. And it should be of ICOR.

DR. PAXTON: All right, Art.

DR. SEDRAKYAN: I wanted to support that. I think what ISAR is already doing really well is the joints. The hip and knees are, you know, very well-developed areas, and it has a very good work group. It has -- you also helped -- I mean, Liz also helped, of course, launch that. Bodett (ph.), and Rob, you're involved in it, right, in the U.K. So, it has like very well established, you know, process for that as well.

What I think is a niche area for ICOR 2.0 is the spine and shoulder, total ankle sort of areas that were not receiving as much attention, because they were not as high, maybe, on agenda before. But now, I think with the leadership of FDA team, Raquel's leadership and Dr. Devlin and others, I think the spine surgery and devices are getting a lot of attention, and yet we don't have a good process to understand what's going on internationally either.

Registries are relatively limited. Kaiser has one of the best, and maybe the best registry in the country that can answer many questions. It would be really good for us to leverage international data and understand performance of the cages that were highlighted

today, for example, some of the aspects, or some of the bone, you know, morphogenic coding products that might be used, and seem to have outcomes that are comparable, and et cetera, but at least better understand their particular uses, where they can provide value for people.

A lot of off-label use, of course that's important also to understand, whether it leads to good outcomes, and if there's small cohorts of patients, it makes it even higher priority to study internationally because limited cohorts can be pulled together.

I just wanted to also highlight the fact that we can do this using HIVE platform because it's GDPR compliant. It helps us. Like an example of that (indiscernible) project, the reason I highlighted, it allowed even German centers to put their data in. And Germany being the most legally difficult in Europe for data collection, we're really proud of that success.

So, I think in this collaboration 2.0 that I hope we can work with Liz and Rob together, we need to identify those niche areas, shoulder, spine, maybe total ankle, and initiate projects in those settings. I know like if Per-Henrik is still on, the Norwegians were quite interested in spine project. They wanted to study the disc arthroplasty device, for example. Another sort of market area which is not commonly done, and there are questions internationally about its performance. So those are the sort of thoughts I have, based on prior discussions.

DR. PAXTON: Danica, your --

DR. MARINAC-DABIC: Yes. I would -- if I could reflect on a couple of things from the FDA, wearing my regulatory hat, I'd like to highlight the importance of regulators in these international collaborations. You know, going back to ICOR successes, I think the presence of FDA and other regulators was really, really important in pulling entire community together. By that time, if you can recall, we had these highly sophisticated Nordic registries

from Scandinavian countries and U.K., and a few others that actually are, they're very successful. And they're on the books, changing the revision rates immensely, cutting in half, based on the data per the national registries.

But others were sort of not necessarily being admitted to that club. What I would have changed, I think was the organization of this role of registries and being able to actually to up the actual quality of all the registries that existed at the time and inspire the countries that didn't have registries to start thinking about them. So that's one thing that I think is important, from FDA, from regulatory perspective.

The other one that I think is important is that ICOR was always envisioning that it was not going to be only about the registries. If you can recall in (indiscernible) documents, we in fact endorsed the concept of international CRNs, meaning that whenever possible we are going to actually link the data coming from registries to other data sources, which was easier in Europe than U.S. at the time. But the idea here is that International Society of Arthroplasty Registries is very important driving force in here. But there is more to it that I think regulators, payers, others that can bring to this collaboration.

So, I would say as we move forward, it has to be a very close collaboration between ICOR and International Society of Arthroplasty Registries, to actually take us to the next level.

DR. PAXTON: Good comment. The ISAR group, many of them have spine as well as shoulder registries, so it seems like a perfect collaboration in terms of a starting point in working with the FDA, including other key collaborators. So, what would the first steps be, in your recommendation?

DR. SEDRAKYAN: Liz, we'll look for your leadership for that too.

DR. PAXTON: Moderator.

DR. MARINAC-DABIC: No, that's so, because of your role. I'm not sure if you're still,

or you're past president until you serve, but you've been actually leader of ICOR for years. And obviously now, with our leaders at the FDA, and we'd like definitely to engage with many more folks across other entities, you know, that were part of the ICOR. There are some good recipe books that we can follow, that actually already have track records of success, I would say.

DR. SEDRAKYAN: Yeah. I remember the watershed moment was in New Orleans, when we were all together, and Stephen Graves and the team, we had just sat down. I don't remember which restaurant was that, and we said, here's the first three projects we want to do. And that was like okay, we're going to do it. So, if you remember how low-cost and efficient process was ICOR, I mean, I think it was remarkable to do so many studies on a low FDA budget. Not to criticize FDA, but it was like we operated -- a lot of work was in-kind from all the partners, and people were enthusiastic about the topics of the research.

It was also kind of opportune moment with the metal-on-metal hip problems emerging. By the way, there was this misconception that ICOR was started because of the metal-on-metal hip problem. It was way after, just to be clear. It was though considered to be a good topic, because it was still lingering and really in a full-blown concern everywhere.

But there isn't such a factor now, but at the same time, there's a lot interest in spine and shoulder, as Rob highlighted, because of, you know, very high acceptance and adoption and concerns about use in off-label settings and potentially outcomes not being as good as we would want them to be. So, if that can energize the international community again to do a lot of work in kind, that would be great. But if we could go back to NIH for funding, that would have been even better.

Or Rob, maybe you can comment about E.U. Horizon 2021 beyond, whether that could be an opportunity also to get some funding after CORPS-MD.

DR. NELISSEN: Yeah. I think that's just a thing, so to do about two things total, two

remarkable things, it's -- would be nice to -- especially for on the spine and the shoulder. A little -- a lot of those spine registries of Europe, they -- I mean in Netherlands, they stopped two years ago. And then it's all about funding, and all -- but it's not only funding, it's also people, the neurosurgeon and all the big surgeries that were a little fight. There are some folks around in Europe, I think Norway, Sweden, but -- and of course, I'm a member of ISAR of course, that makes sense. But in Eurospine they also stopped. It might be the U.S. Spine Consortium, but Eurospine, that size amazes me.

So, a big push. So, that means, actually, there are very few metrics around, which are really evidence-based. The difficulty with hips and knees was, well the knee registry is around since '74. Well, sadly of course, Otto died. The hip registry was in Sweden, around since '79. And there were the new ones like the U.K. and Wales and Netherlands. We have better metrics like (indiscernible) et cetera, but it was really, the way of analysis was really set by the Scandinavians.

Well, so and the opportunity now is for shoulder and spine to have a new way of evaluating these things. With my group, you have a lot of those progenies, yes, this year and last year about X book outcome things, so like more a conglomerate way of evaluating. And that's the way forward. So, we can't only do this analysis like ICOR, but we can also show the -- well, doctors, regulators again, what are important metrics for evaluating in an evidence-based way?

And then, when we are now in an associate way of thinking, in the Netherlands, which is very good, is a very important issue in the Netherlands is now choosing wisely. I think it's also in the U.S., and Australia, because a lot of surgeries are being done for nonsense, where the outcome with conservative is as good as surgery. So, and when you look at the global health increase, in the Netherlands they expect when it goes this way exponentially, one -- 35% of all people in Netherlands won't work in healthcare.

And that's your two factor because there's a huge technology push. I do a lot of technology surgeries today, so I'm in favor of this, but we really need to evaluate it. So, I think that's also -- I think the great opportunity of ICOR 2.0, or and CORE-MD, whatever you call it, that's -- I don't care. But an intellectual challenge will be to set the pace for the best way of evaluating. I think that's --

DR. PAXTON: And I just -- great. Thank you for your comments. I just wanted to highlight something both Rob and Art touched on, and that's the importance of the clinical question that we would be investigating, because registries have limited bandwidth. So, it has to be an important clinical question that can impact quality of care for patients, for the incentive to be there. So, we can explore how to go about defining those clinical questions, potentially doing that at the ISAR Congress meeting next week as a first step.

And on that note, I will go ahead and close the session, and we'll move on to closing remarks.

DR. MARINAC-DABIC: Thank you, Liz, very much. And thank you to all the speakers. Please stay on camera. We would like to take some very fun picture at the end, to illustrate and remember this important conference. I would like to thank all the speakers and panelists for their outstanding presentations and for the rich discussion throughout the entire conference. And also, to the Planning Committee of the FDA and MDEpiNet for meeting, organization of the meeting, and also to all the participants that we had today. Thank you for your attention, and thoughtful engagement.

And it's my great pleasure now to introduce Dr. Daniel Caños, the director of the Office of Clinical Evidence to give the closing remarks.

DR. CAÑOS: Thank you very much. This has been an exciting day of information sharing, engaged discussion and planning steps for future collaborations. There is a palpable energy in our stakeholder community. Today we had 200 registrants and close to

150 people in attendance at all times throughout the day. The start began with where the focus of our work is, and that is on the patients.

The FDA, NIH and Cornell discussed the importance of studying the impact of orthopedic therapies in all patients, recognizing that there are possible differences in longer-term performance associated with device wear, important considerations including sex differences, inclusions -- and the need for inclusions of subgroups with sufficient size to allow for meaningful conclusions.

We also spoke about the importance of our work in eliminating health disparities, and taking a personalized medicine focus approach to solutions, and thinking about ways to address these challenges, and generating the evidence throughout the total product life cycle.

We heard from industry, that emphasized the importance of flexibility, and data sources, including considerations for U.S. data. CAPT Peat highlighted the great work being done by Kaiser, and the potential for sources like Kaiser and ASR to address research questions and importantly, identify new questions for the field to address. In bringing these data sources together, our group discussed the merit of harmonization of efforts in data collection with NIH, other federal partners, and the rest of the stakeholder community, both national and international.

We also heard about innovative platforms designed to facilitate the clinical trial enterprise. MDEpiNet presented on HIVE, the innovative platform designed to improve patient engagement, collaboration between patients and physicians, targeting the overall efforts in patient follow-up and data completeness, but I think most importantly, improving engagement between patients and clinicians.

CAPT Peat mentioned the patient-facing mobile app development in orthopedics, which is based on the work that NEST originally funded through their test cases for

developing patient-facing apps for capturing the patient-reported outcome data. The importance of decentralized trial tools like this have been abundantly clear throughout COVID, where direct patient follow-up has been very difficult. Further, NEST and others highlighted the power of bringing other data sources. We saw presentations from FDA and others on claims data, bringing in CMS data, private payer data, integrated into health system information while preserving privacy, as Dr. Marinac-Dabic highlighted in her last section, through distributed data networks, and using tokenization, like vendors such as DataVance and others.

This work has been successfully shown to be executed through NEST test cases. And so, in our last session with Dr. Nelissen, Marinac-Dabic, Sedrakyan and others, we covered the international efforts, and in similar activities across other device areas where lessons can be learned, end up maximizing the information in hand, and maximize the impact of our work.

This all brings it back to the patient, where we are generating real-world evidence through the total product life cycle and integrating patient-reported outcomes data for decision making, and ultimately providing this to patients and providers, facilitating patient-shared decision making, informed decision making.

The last session did a great job of bringing this all together, right, highlighting the next steps, providing real opportunities for synergy. I think we really hit upon some great areas for those next steps.

I join Dr. Marinac-Dabic in thanking everyone for their participation today, including all the invited speakers, the panelists, as well as OHT 6, OCEA, MDEpiNet for their work in planning, organizing and leadership for this meeting. I thank you all very much for joining in today. Have a great rest of your day.

(Whereupon, at 4:36 p.m., the meeting was adjourned.)

1

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

VIRTUAL PUBLIC MEETING - ORTHOPEDIC STRATEGICALLY COORDINATED REGISTRY NETWORK (ORTHO CRN)

Via Videoconference

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

_____

TOM BOWMAN

Official Reporter

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947