BEFORE THE
SCIENTIFIC AND MEDICAL ACCOUNTABILITY
STANDARDS WORKING GROUP
TO THE
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
ORGANIZED PURSUANT TO THE
CALIFORNIA STEM CELL RESEARCH AND CURES ACT

REGULAR MEETING

LOCATION:	LUXE HOTEL 11461 W. SUNSET BOULEVARD LOS ANGELES, CALIFORNIA
DATE:	FEBRUARY 17 AND 18, 2009
REPORTER:	BETH C. DRAIN, CSR CSR. NO. 7152
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LOS ANGELES, CALIFORNIA;

WEDNESDAY, FEBRUARY 18, 2009

9 A.M.

CHAIRMAN LO: GOOD MORNING. I'D LIKE TO CALL US TO ORDER. FIRST I WOULD HAVE SAID I THOUGHT YESTERDAY'S DISCUSSION WAS REALLY INTERESTING, AND THEY'RE TOUGH ISSUES, CONTROVERSIAL ISSUES, AND I THINK WE MADE A GOOD START. WE HAD SOME MORE DISCUSSION LAST NIGHT.

IN LOOKING AT THE SCHEDULE TODAY, I'M WONDERING IF WE REALLY CAN FINISH BEFORE 3 O'CLOCK. LET ME MAKE A SUGGESTION, THAT IF WE WORK THROUGH -- WE TAKE A BREAK AT ABOUT ELEVEN TO CHECK OUT AND EVERYTHING AND WORK THROUGH TILL ONE AND THEN HAVE LUNCH AT ONE. THOSE OF YOU WHO WANT TO TRY AND EXIT AT ONE, I THINK WE SHOULD BE DONE BY THEN. WE DON'T HAVE ANY ITEMS OF BUSINESS LEFT OVER FROM YESTERDAY. SO I THINK WE CAN HAVE OUR THREE SPEAKERS, A RICH DISCUSSION WITHIN THREE AND A HALF HOURS SO WE CAN BE DONE BY ONE AND HAVE LUNCH AFTERWARDS FOR THOSE WHO WANT TO STAY OR CAN STAY. DOES THAT SOUND REASONABLE? DOES ANYBODY OBJECT TO FINISHING EARLY?

DR. LOMAX: ONE OTHER ITEM, THE LUNCHES

CAN BE AVAILABLE TO PACK A SANDWICH OR SOMETHING TO GO IF YOU LIKE AS WELL FOR TRAVELING. SO IF THAT IS OF INTEREST, LET PAT BECKER KNOW, AND SHE CAN ARRANGE -- THEY CAN BOX SOMETHING UP FOR YOU. IT WILL BE KIND OF A SANDWICH PLATTER.

CHAIRMAN LO: THEY'VE DONE THAT BEFORE, AND IT'S ACTUALLY QUITE GOOD FOR AIRPORT FOOD.

OKAY. I WANT TO JUST START BY TRYING TO SORT OF SUM UP SOME OF WHAT WE DID YESTERDAY AND TO HAVE SOME -- MAKE A FEW TENTATIVE SUGGESTIONS. AS YOU KNOW, ONE OF THE THINGS WE WANT TO DO IS TO TRY AND THINK THROUGH WHAT, IF ANYTHING, SHOULD CIRM BE DOING IN ADDITION TO WHAT IRB'S NOW DO IN ADDITION TO WHAT THE FDA DOES.

SO FIRST I JUST WANTED TO SAY THAT WE REALLY SORT OF TALKED ABOUT SORT OF THE BASIC ETHICAL ISSUES WITHOUT MAYBE MAKING IT REALLY EXPLICIT. AND I THINK WE ALL UNDERSTOOD YESTERDAY THAT WHAT MAKES EARLY PHASE CLINICAL TRIALS SO DIFFICULT AND ETHICALLY COMPLICATED IS THAT PARTICIPANTS UNDERGO THE RISK OF AN INNOVATIVE INTERVENTION WHERE GOING INTO A PHASE I STUDY, YOU DON'T KNOW WHAT THE SAFETY AND EFFICACY OF THE INTERVENTIONS ARE. IT COULD BE WORSE THAN DOING NOTHING OR A PLACEBO. IF SOMEONE COULD JUST PUSH

THE SLIDE TO THE NEXT SLIDE.

AND, YOU KNOW, IF YOU THINK ABOUT CLINICAL TRIAL ETHICS, THE FUNDAMENTAL CONSIDERATIONS ARE, FIRST, THE RISK-BENEFIT RATIO HAS TO BE ACCEPTABLE. NOW, WHAT MAKES IT HARD IN PHASE I AND PARTICULARLY IN STEM CELLS IS THE RISKS ARE UNCERTAIN. WE'RE DOING SOMETHING FOR THE FIRST TIME. WE CAN'T REALLY SAY WHAT THE RISKS ARE. AND SECONDLY, THERE HAS TO BE INFORMED CONSENT. AND WE TALKED A LITTLE BIT YESTERDAY ABOUT HOW INFORMED CONSENT IN GENERAL IS HARD BECAUSE PEOPLE, PARTICIPANTS, BELIEVE THAT THE DOCTOR IN HER HEART OF HEARTS WOULDN'T BE OFFERING INTERVENTION IF SHE DIDN'T KNOW IT REALLY WORKED. NO MATTER WHAT THE INFORMED CONSENT FORM SAYS ABOUT WE DON'T KNOW, PARTICIPANTS, IF YOU ASK THEM AFTERWARDS, SAY BUT THEY REALLY, REALLY THINK IT'S GOING TO WORK. AND SO, THEREFORE, IT'S GOING TO HELP ME.

AND IT'S PARTICULARLY, I THINK, THE CASE BECAUSE THE HOPES ARE SO HIGH WITH STEM CELL RESEARCH. AND THESE ARE SERIOUS DISEASES FOR WHICH THERE ARE REALLY NO GOOD THERAPIES.

WE TALKED A LOT ABOUT SHAM SURGERY, AND IT'S CONTROVERSIAL AND IT'S COMPLICATED. AND THERE ARE REASONS THAT YOU MIGHT WANT TO DO IT, AND THERE

ARE REAL REASONS TO SAY, GOSH, THAT'S AWFUL. THERE IS A VERY INTERESTING E-MAIL EXCHANGE THAT ALTA STARTED AND JOSE DID AND I SORT OF SENT SOME THINGS AROUND SO WE ACTUALLY PULLED SOME PDF'S FOR YOU. THERE ARE A NUMBER OF ARTICLES ON SHAM SURGERY IN PARKINSON'S DISEASE, WHICH I THINK IS SOMETHING THAT WE MIGHT ACTUALLY BE DEALING WITH AT CIRM.

ONE EDITORIAL WHICH I SENT YOU FRAMED IT AS A CHOICE OF TWO EVILS. SO IT'S A DILEMMA PRECISELY BECAUSE THERE ARE REASONS TO DO BOTH ONE THING AND ITS OPPOSITE. AND THE ISSUES THAT WERE LAID OUT WERE IF YOU DON'T -- IN SOME SITUATIONS IF YOU DON'T DO SHAM SURGERY, YOU MAY NOT BE ABLE TO RIGOROUSLY EVALUATE THE SAFETY AND EFFICACY OF AN INTERVENTION. IN SITUATIONS WHERE THE SURGERY ITSELF CAN INDUCE EITHER, AS BRUCE DOBKIN SUGGESTED, SHAM SURGERY MAY ACTUALLY BE AN ACTIVE INTERVENTION BY DISRUPTING NEUROCIRCUITS, OR IT MAY INSTILL BELIEF THAT YOU HAD SOMETHING ACTIVE DONE THAT WILL CHANGE YOUR BEHAVIORS OR YOUR ABILITY TO PERFORM THE OUTCOME MEASURES.

ON THE OTHER HAND, YOU CLEARLY ARE UNDERGOING A RISK BY HAVING SURGERY DONE, THE ANESTHETIC RISK, THE SURGICAL RISK, AND SO FORTH. AND AS SHERRY POINTED OUT, THERE'S AN INTUITIVE

LEVEL WHERE IT SEEMS WRONG TO SAY TO SOMEONE WE'RE GOING TO HAVE YOU UNDERGO SOMETHING THAT WE KNOW HAS RISK AND WE DON'T EXPECT IT TO HELP YOU OTHER THAN YOUR BELIEVING IT'S GOING TO HELP YOU.

NOW, THERE ARE TWO OTHER EMPIRICAL ARTICLES I THOUGHT WERE INTERESTING, BOTH ON PARKINSON'S DISEASE SURGICAL INTERVENTIONS THAT WERE PLACEBO SURGERY. ONE WAS A SUMMARY OF PUBLISHED LITERATURE SHOWING THAT IN PARKINSON'S DISEASE, PEOPLE WHO GOT THE SHAM SURGERY ACTUALLY DID BETTER THAN PEOPLE WHO GOT THE ACTIVE SURGERY. OKAY. AND THE SECOND STUDY WAS A WILLINGNESS TO ENROLL A SURVEY OF PEOPLE WITH PARKINSON'S DISEASE AND OTHER DISEASES. AND WHEN IT WAS EXPLAINED TO THEM, THE MAJORITY OF THE PARTICIPANTS SAID THEY WOULD BE WILLING TO ENTER A SHAM SURGERY TRIAL.

THERE IS ANOTHER STUDY THAT I SENT YOU WHICH WAS SORT OF AN OVERVIEW BY FRANK MILLER AT NIH, AND HE SUGGESTED THAT MAYBE THE QUESTION IS NOT DO WE EVER ALLOW SHAM SURGERY OR DO WE ALWAYS NEED SHAM SURGERY. HE SAID IF YOU LOOK AT THE DISEASE AND THE INTERVENTION, THERE ARE A SERIES OF CONSIDERATIONS YOU NEED TO THINK ABOUT. CAN YOU WITHOUT THE SURGICAL INTERVENTION INDUCE THE BELIEF THAT YOU HAD SOMETHING VALUABLE DONE? AND I WOULD

ARGUE THE BELIEF THAT YOU'RE GOING TO RETRAIN YOURSELF, EXERCISE, GO TO REHAB HAS BEEN IN A WAY THAT CAN BE BENEFICIAL. HE SAID YOU HAVE TO LOOK AT THE RISKS OF THE SHAM SURGERY. IS IT ACCEPTABLE, THEY ARE MINIMIZED, AND SO FORTH. SO IT WAS A MORE NUANCED DISCUSSION THAN IT'S ALWAYS GOOD, IT'S ALWAYS BAD.

I ALSO WANT TO SUGGEST THREE THINGS WE MIGHT WANT TO THINK ABOUT AS POSSIBLE, AND UNDERLINE POSSIBLE, ITEMS WE MIGHT WANT TO SUGGEST AS THINGS FOR THE ICOC TO DO. ONE, WHICH WE ALREADY TALKED ABOUT YESTERDAY, I THINK, JOSE, THIS IS IN RESPONSE TO A QUESTION YOU ASKED, TO HAVE CIRM BE ONE OF THE CONVENERS OF A STATE-OF-THE-ART MEETING TO DEVELOP A CONSENSUS ON WHAT SHOULD BE REQUIRED FOR PRECLINICAL TESTING. IT REALLY ADDRESSES JOSE'S CONCERN THAT AS AN INVESTIGATOR, IF YOU GO TO THE FDA AND SAY WHAT DO I NEED TO DO TO GET THROUGH YOUR PRECLINICAL REVIEW, THEY WON'T GIVE YOU A FLAT-OUT ANSWER UNTIL YOU SORT OF HAND THEM A PROTOCOL AND SAY. THEY'LL SAY, WELL, WE WANT A FEW MORE SPECIES OR A FEW MORE SUBJECTS. IT WON'T SAY SO-AND-SO TRIED THIS AND WE'RE GOING TO HAVE TWO SPECIES NOW RATHER THAN ONE.

SO THIS WAS A SUGGESTION THAT MIGHT HELP THE FDA BE MORE PROACTIVE IN LETTING INVESTIGATORS

KNOW WHAT THEY NEED TO DO. AND IT COULD MAKE RESEARCH MORE EFFICIENT IF THE INVESTIGATORS DIDN'T HAVE TO GUESS AND FALSE START. SO THAT'S A SUGGESTION. AND THEN THAT COULD BE DONE IN CONJUNCTION WITH OTHER UNIVERSITIES DOING STEM CELL RESEARCH LIKE WISCONSIN OR PERHAPS IN CONJUNCTION WITH ISSCR.

SECOND SUGGESTION IS SHOULD WE, AS A CONDITION OF CIRM FUNDING, HAVE SOME REQUIREMENT FOR TIMELY DISSEMINATION OF FINDINGS, INCLUDING NEGATIVE FINDINGS FROM AN EARLY CLINICAL TRIAL? AND AGAIN, THIS IS A LITTLE COMPLICATED BECAUSE UNLESS OTHER SCIENTISTS KNOW NEGATIVE RESULTS FROM A PREVIOUS TRIAL, IT'S GOING TO BE HARD FOR THEM TO GAUGE THE SAFETY OF AN INTERVENTION THEY'RE PLANNING OR TO IMPROVE ON AN INTERVENTION THAT WAS TRIED BEFORE AND DIDN'T WORK.

ON THE OTHER HAND, CLEARLY THERE ARE SOME COMPANIES THAT IF THEY HAVE A NEGATIVE STUDY, WILL NOT WANT IT SHARED BECAUSE OF THE ADVERSE IMPACT ON THEIR VIABILITY IN SOME CASES.

AND THE THIRD SUGGESTION I WANT US JUST TO PERHAPS CONSIDER, THINK ABOUT IS THE CONSENT ISSUE. SO THAT WE MIGHT SAY IF YOU REALLY, REALLY WANTED TO MAKE SURE THAT PARTICIPANTS IN AN EARLY PHASE STEM

CELL CLINICAL TRIAL KNEW WHAT THEY WERE GETTING INTO, SHOULD WE HAVE SOME SORT OF ASSESSMENT OF THE PARTICIPANT'S APPRECIATION OF KEY ASPECTS OF THE TRIAL? AND THOSE MIGHT BE WE DON'T KNOW WHETHER THIS IS GOING TO WORK. IT MIGHT MAKE YOU WORSE, ETC., REALLY SORT OF KEY ISSUES THAT WE STRUGGLED WITH YESTERDAY.

THIS WOULD SHIFT OUR NOTION OF CONSENT FROM DISCLOSURE IN THE CONSENT FORM TO UNDERSTANDING BY THE PARTICIPANT, AND IT'S CONSISTENT WITH WHAT WE SAID WITH OOCYTE DONATION. WHEREAS, YOU REMEMBER WE SAID WOMEN DONATING REALLY, WE NEED TO REALLY UNDERSTAND -- BE SURE THEY UNDERSTAND THE RISKS AND THE PROCEDURES. SO THAT'S BACKGROUND FOR US.

NOW WE HAVE A REALLY GREAT SET OF SPEAKERS WHO HAVE GRACIOUSLY COME HERE TODAY TO SHARE THEIR EXPERTISE AND DISCUSS WITH US. MICHAEL KALICHMAN IS GOING TO GO FIRST. HE'S PROFESSOR OF MEDICINE AT UCSD. HE'S ACTUALLY BEEN HERE BEFORE BECAUSE HE DIRECTS THE SCRO AT UCSD AND HAS BEEN WRITING ABOUT ETHICS OF RESEARCH IN GENERAL AND STEM CELL RESEARCH ETHICS IN PARTICULAR. SO MICHAEL WILL START, AND THEN WE'LL HAVE TWO OTHER SPEAKERS I'LL INTRODUCE LATER. MIKE, THANKS FOR COMING.

DR. KALICHMAN: THANKS VERY MUCH. AND I

WASN'T HERE YESTERDAY, BUT FROM WHAT I'VE HEARD AND ADDING TO THAT, BERNIE'S REMARKS NOW, MUCH OF WHAT I'M GOING TO COVER HAS ACTUALLY, I THINK, BEEN COVERED. BUT I WILL -- I'VE TAKEN OUT SOME OF THE SLIDES THAT YOU HAVE IN YOUR BROCHURES, SO THESE AREN'T ALL IN THERE ANYMORE BECAUSE THEY WEREN'T ALL NECESSARY. AND WHAT I'M GOING TO BE SAYING IS BASED IN PART ON A PAPER THAT PHIL SCHWARTZ ROPED ME INTO HELPING WITH THAT WILL BE IN *AMERICAN JOURNAL OF BIOETHICS*, AN OPEN PEER COMMENTARY.

IN THIS CASE WE WERE LOOKING AT CELL-BASED INTERVENTIONS, NOT SPECIFICALLY STEM CELL RESEARCH, CELL-BASED INTERVENTIONS FOR THE CENTRAL NERVOUS SYSTEM. AND WE CAME UP WITH SOME SUGGESTIONS AND THOUGHTS ABOUT THE SPECIAL ISSUES THAT THIS RESEARCH RAISED. AND I'VE TRANSLATED THAT A BIT INTO THE ISSUES THAT WE'RE THINKING ABOUT IN CALIFORNIA FOR STEM CELL RESEARCH.

JUST AS BACKGROUND, BEFORE I GO INTO SOME SUGGESTIONS, SOMETHING THAT I THINK IS CLEAR FROM DISCUSSION EVERYBODY HAS ALREADY HAD AND THINKING ABOUT, WHAT WE'RE TALKING ABOUT HERE IS SOMETHING WHEN YOU'RE IN A CLINICAL TRIAL, UNLIKE MANY OTHER KINDS OF CLINICAL TRIALS, WHEN YOU PUT CELLS INTO SOMEBODY'S BRAIN OR BODY, YOU HAVE SOMETHING THAT'S

NO LONGER REVERSIBLE. IT'S IRREVERSIBLE. YOU CAN'T HAVE SOMEBODY DECIDE HALFWAY THROUGH THAT TRIAL I'VE DECIDED I DON'T WANT TO BE IN THE TRIAL BECAUSE YOU CAN'T GO IN AND TAKE THOSE CELLS OUT, AT LEAST NOT READILY.

HOWEVER, THE OBLIGATIONS WE HAVE FOR THIS KIND OF RESEARCH ARE SIMILAR TO THE OBLIGATIONS FOR ANY KIND OF CLINICAL TRIALS. WE SHOULD BE SURE BEFORE WE PROCEED TO THE CLINICAL TRIAL THAT, SINCE WE AREN'T CERTAIN THAT THIS IS GOING TO BE EFFECTIVE OR SAFE, WE WANT TO HAVE STANDARDS THAT ARE HIGH ENOUGH SO THAT WHEN WE DO GO TO THAT TRIAL, WE HAVE AT LEAST A REASONABLE CHANCE OF NOT DOING ANTICIBLE HARM, HARM THAT WE COULD HAVE ANTICIPATED. AND SECOND, YOU WANT TO SUFFICIENTLY INFORM YOUR SUBJECTS, AS BERNIE WAS JUST TALKING ABOUT.

SO THERE ARE RISKS OF GOING INTO ANY KIND OF CLINICAL RESEARCH, AND THE RISKS ARE GREATER WHEN YOU'RE GOING INTO A NEW AREA AS WE ARE STEM CELL RESEARCH. BUT THE ANSWER TO THE QUESTION OF SHOULD WE STOP THIS RESEARCH IS ABSOLUTELY NO. BUT THE STANDARDS OF MEDICAL RESEARCH DO CALL FOR US TO BE SURE THAT WE DON'T INTENTIONALLY DO HARM AND, SECONDLY, THAT WE SHOULD AVOID THE CHANCE OF DOING GOOD SOLELY BECAUSE OF THE POSSIBILITY OF HARM.

SO SHOULD WE TEST FOR EVERYTHING? AND THIS IS IN PART WHY PHIL SCHWARTZ AND I WROTE OUR ARTICLES. WE WERE RESPONDING TO THE TARGET ARTICLE FOR *AMERICAN JOURNAL OF BIOETHICS*. IT WAS ARGUING FOR A PRETTY RIGOROUS BATTERY OF TESTS TO BE DONE ON ALL PEOPLE WHO RECEIVE CELL-BASED INTERVENTION FOR THE NERVOUS SYSTEM. AND IT OCCURRED TO US THAT THOSE TESTS, ALTHOUGH THEY MIGHT GIVE US A SENSE OF FEELING BETTER, THAT WE'RE DOING THE RIGHT THING BECAUSE WE'RE TESTING FOR ANY POSSIBLE PROBLEMS. SUCH TESTS ARE VERY COSTLY IN TERMS OF THE NUMBER OF SUBJECTS YOU HAVE TO HAVE, THE MONEY AND EFFORT INVOLVED, AND THE TIME INVOLVED. AND YOU WANT TO BE SURE BEFORE YOU GO INTO SUCH TESTS THAT THEY ACTUALLY WILL SOLVE THE PROBLEM YOU'RE TRYING TO SOLVE.

SO BEFORE BEGINNING SUCH TESTING, WE'RE ARGUING THAT ONLY WHEN DATA FROM PRECLINICAL STUDIES OR OTHER CLINICAL TRIALS PROVIDES REASON TO PREDICT THAT A PARTICULAR KIND OF A PROBLEM IS LIKELY SHOULD YOU THEN GO TO THAT EXTRAORDINARY LEVEL OF DOING THAT EXTRA TESTING ON TOP OF WHAT YOU ALREADY WERE PLANNING.

SO THE BULK OF MY PRESENTATION IS GOING TO BE PROPOSING SEVERAL THINGS. THESE ARE NOT FINAL

IDEAS, BUT SOME IDEAS TO PUT ON THE TABLE OF THINGS THAT WE MIGHT WANT TO CONSIDER FOR STEM CELL-BASED RESEARCH.

FIRST ONE IS THAT WHEN WE TALK ABOUT ANIMAL STUDIES, WHICH ARE STANDARD FOR ANY KIND OF NEW CLINICAL TRIALS TO BE IN PLACE IN THE FIRST PLACE BECAUSE THESE INTERVENTIONS THAT WE'RE DEALING WITH CLINICALLY ARE LIKELY TO BE IRREVERSIBLE, THE STANDARD FOR OUR PRECLINICAL DATA, THAT MEANS THE DATA THAT WE OBTAIN FROM ANIMAL STUDIES, SHOULD BE HIGHER THAN FOR OTHER INTERVENTIONS. WE'RE NOT QUANTIFYING THIS BY SAYING HOW MUCH HIGHER, BUT WE ARE SAYING THAT WE SHOULD LOOK FOR SOMETHING MORE THAN WE NORMALLY WOULD IN A TRIAL, THAT SOMEBODY COULD SAY, WAIT, THIS ISN'T WORKING OUT WELL. I DON'T WANT TO CONTINUE.

SECOND, WE SHOULD HAVE A BETTER SENSE OF THE MECHANISMS BEFORE WE GO INTO THE TRIAL. IN MANY CASES IT'S ENOUGH TO KNOW THAT SOMETHING WORKS. YOU HAVE SOME SENSE IN ANIMAL STUDIES BASED ON OTHER EXPERIENCE THIS MIGHT WORK EVEN IF YOU DON'T REALLY UNDERSTAND COMPLETELY WHY IT WORKS. WE'RE NOT ARGUING THAT WE HAVE TO UNDERSTAND EVERYTHING ABOUT MECHANISMS, BUT HAVING SOME MECHANISTIC SENSE THAT THERE IS AN EXPLANATION FOR THE DISEASE THAT WE

UNDERSTAND, AN EXPLANATION FOR HOW THE TREATMENT MIGHT WORK, AND BE BETTER THAN NOT DOING SOMETHING IS THE SECOND STANDARD WE'RE ARGUING WE SHOULD INVOKE.

THIRD, ESPECIALLY AT THE EARLIEST STAGES OF TREATMENT, WE SHOULD LOOK AT THOSE DISEASES AND CONDITIONS THAT ARE UNTREATABLE AND SEVERELY DEBILITATING RATHER THAN THINGS THAT MAY BE HANDLED IN OTHER WAYS OR MAY NOT BE AS SEVERE. THIS BECOMES A REALLY KEY POINT. BERNIE WAS JUST TALKING ABOUT SOMETHING THAT MANY OF US HAVE TALKED ABOUT OFTEN, AND THAT'S THAT WHEN YOU GO TO A CLINICAL TRIAL, YOU'RE NOT DOING IT BECAUSE YOU KNOW SOMETHING IS SAFE AND EFFECTIVE. YOU'RE DOING IT BECAUSE YOU DON'T KNOW. AND EVEN THOUGH SOMEBODY IS SUFFERING FROM A DISEASE, SOMETIMES TERRIBLY SUFFERING FROM THAT DISEASE, THE PRESUMPTION THAT ANYTHING IS BETTER THAN NOTHING IS NOT ALWAYS TRUE.

THERE ARE CASES EVEN I'VE HEARD ABOUT THE EXAMPLE IN MELANOMA CLINICAL TRIALS WHERE PEOPLE ARE GOING TO DIE AND DIE IN A DIFFICULT WAY BECAUSE OF THE CANCER. THEY'VE GONE INTO CLINICAL TRIALS AND FOUND IT WAS PREFERABLE TO BE IN THE PLACEBO GROUP THAN IN THE TREATMENT GROUP. SO YOU DON'T KNOW THAT THIS IS GOING TO BE BETTER. AND UNDER THOSE

CONDITIONS, YOU PROBABLY WANT TO ERR ON THE SIDE OF CAUTION BEFORE HAVING PEOPLE ENTER TRIALS. AND THEREFORE, WE WOULD ARGUE THAT WE SHOULD BEGIN BY RESTRICTING INITIAL TRIALS WITH STEM CELL THERAPIES TO THOSE DISEASES AND DISORDERS WITH HIGH LEVELS OF MORTALITY AND/OR MORBIDITY AND THAT COULD HELP BALANCE THE UNKNOWN RISKS OF GOING IN THIS NEW DIRECTION AGAINST THE KNOWN HARMS OF THE PARTICULAR ILLNESS.

FOURTH, A ROBUST INFORMED CONSENT PROCESS, BUT I'M GOING TO GO FURTHER THAN BERNIE JUST WENT BY SAYING THAT WE USUALLY THINK ABOUT INFORMED CONSENT BEING A PROCESS FOR THE SUBJECT WHO IS GOING TO BE ENTERING THE RESEARCH. AND WHAT WE'RE SUGGESTING IS THAT WE NEED TO THINK OF A MORE ROBUST WAY OF THINKING ABOUT INFORMED CONSENT, THAT THIS INVOLVES NOT JUST THE SUBJECTS OF THE RESEARCH, THE POTENTIAL PATIENTS AS WE START USING THE THERAPIES THAT MIGHT COME OUT OF THOSE TRIALS, THE TREATING PHYSICIANS FOR THOSE PATIENTS, AND EVEN THE RESEARCHERS CONDUCTING THE CLINICAL TRIALS SO THAT THEY ALL UNDERSTAND THAT WE ARE WORKING IN UNCHARTERED TERRITORY AND THAT WE MIGHT FIND THINGS THAT WE JUST HADN'T EVEN ANTICIPATED THAT COULD BE PROBLEMS.

IT'S THAT UNANTICIPATED ISSUE THAT WE NEED

TO WATCH FOR, SO ANY ANOMALIES THAT WERE UNANTICIPATED MIGHT BE CALLED TO OUR ATTENTION AND REPORTED, MEANING THAT WE NEED TO BE DOING MONITORING, NOT JUST DURING THE TRIALS, BUT DURING THE CLINICAL PHASE.

AND THAT LEADS TO THIS FIFTH OBSERVATION OR PROPOSAL, WHICH IS THAT THAT KIND OF ANECDOTAL INFORMATION IS NOT RANDOMIZED CLINICAL TRIAL, BUT IT IS INFORMATION THAT CAN HELP US UNDERSTAND WHERE THE PROBLEMS MIGHT BE. AND THEN BASED ON THOSE OBSERVATIONS OF EVENTS OF CONCERN THAT HAVE OCCURRED DURING THE TRIALS OR MAYBE ARE OCCURRING LATER ONCE THE THERAPY IS IN THE CLINICS, THOSE OBSERVATIONS SHOULD BE ACCUMULATED AND THEN SUBSEQUENTLY IN CLINICAL PRACTICE IN A WAY THAT WE CAN THEN DESIGN BETTER FUTURE TRIALS AND FUTURE PROJECTS SO THAT WE CAN HOPEFULLY AVOID THE RISK THAT WE'VE DISCOVERED ALONG THE WAY.

SIXTH, PROSPECTIVE STUDIES SHOULD TEST FOR PLAUSIBLE RISKS. AND THIS IS BASED ON THAT ANECDOTAL INFORMATION. SO ONCE YOU'VE GOTTEN THAT ANECDOTAL INFORMATION, THE DECISION TO CONDUCT ANY STUDIES OF POTENTIAL ADVERSE EVENTS SHOULD BE BASED ON EVIDENCE. WE SHOULDN'T JUST SAY WE'RE GOING TO DO SOMETHING IN THE BRAIN. WE NEED TO TEST FOR ALL

POSSIBLE NEUROPSYCHOLOGICAL OUTCOMES IN EVERY CLINICAL TRIAL. THAT, WE'RE ARGUING, WOULD BE PROHIBITIVELY EXPENSIVE AND MAYBE WILL ACTUALLY CAUSE US TO THINK WE'RE CAPTURING EVERYTHING WHEN WE AREN'T. SO INSTEAD, BASE OUR DECISION ABOUT WHAT EXTRA THINGS NEED TO BE DONE ON EVIDENCE. AND THAT EVIDENCE WOULD COME FROM THE ANIMAL STUDIES THAT TOLD US WHAT WE MIGHT EXPECT FROM A MECHANISTIC EXPLANATION THAT WOULD TELL US WHAT WE MIGHT EXPECT ABOUT HOW THESE TREATMENTS MIGHT WORK OR NOT AND THE ANECDOTAL OBSERVATIONS THAT WE'VE COLLECTED DURING CLINICAL TRIALS OR APPLICATIONS.

FINAL POINT ABOUT WHAT WE SHOULD DO WAS NOT ACTUALLY IN OUR PAPER, BUT ONE THAT OCCURS TO ME THAT WE SHOULD THINK ABOUT AS WE LOOK AT THESE ISSUES IS THAT THERE ARE TWO META RISKS, RISKS AT A HIGHER LEVEL THAT WE'RE LOOKING AT. ON THE ONE SIDE, IGNORANCE OF THE SPECIAL RISKS OF THESE KINDS OF CELL-BASED INTERVENTIONS COULD RESULT IN SERIOUS SETBACKS IN THIS FIELD OF RESEARCH. IF ERRORS ARE MADE WITH THE FIRST TRIALS, WE GO TOO SOON INTO THOSE TRIALS, AND SERIOUS PROBLEMS DEVELOP, THE PUBLIC, LEGISLATORS, EVEN RESEARCHERS ARE GOING TO STEP BACK QUICKLY FROM WHAT WE'RE DOING, AND WE MAY ACTUALLY LOSE TIME AND LOSE SUCCESS IN THIS FIELD

BECAUSE WE HAD JUMPED TOO FAR TOO QUICKLY.

BUT ON THE OTHER HAND, IF WE PLACE EXCESSIVE HURDLES IN FRONT OF WHAT WE'RE DOING, THAT IS ALSO LIKELY TO IMPEDE PROGRESS. SO EITHER OF THOSE ERRORS RISK SLOWING OF PROMISING NEW TECHNOLOGY, AND THAT CAUSES HARMS, WHICH INCLUDES RESTRICTING OPPORTUNITIES FOR CLINICAL TRIALS THAT COULD BE HELPFUL AND DENYING PATIENTS NEW THERAPEUTIC OPTIONS.

SO IN SUMMARY, WE'RE PROPOSING THAT THE STANDARDS OF EVIDENCE BEFORE GOING INTO TRIALS IN HUMANS SHOULD INCLUDE ANIMAL STUDIES AND BETTER MECHANISTIC EXPLANATIONS THAN WE WOULD USUALLY EXPECT FOR ANY OTHER CLINICAL TRIAL. WE'RE ASKING FOR THE CONDUCT OF THESE INITIAL PHASE I TRIALS WHERE WE JUST WANT TO SEE IF SOMETHING IS SAFE, THAT THAT SHOULD PROBABLY FIRST BEGIN WITH SEVERE UNTREATABLE CONDITIONS, NOT THINGS AT A LOWER LEVEL.

FOURTH, WE SHOULD ENHANCE THE INFORMED CONSENT PROCESS TO INCLUDE NOT JUST THE SUBJECTS OF THE RESEARCH, BUT EVERYBODY INVOLVED TO HELP THEM UNDERSTAND THAT THEY'RE ENTERING UNCHARTERED TERRITORY, SOMETHING WHERE WE DON'T KNOW WHETHER THIS IS GOING TO WORK OR NOT, WHETHER IT'S GOING TO BE SAFE OR NOT, AND THAT IT IS IRREVERSIBLE ONCE WE

START THAT TRIAL.

FIFTH, WE SHOULD COLLECT ANECDOTAL INFORMATION AND USE THAT FOR EVIDENCE-BASED TESTING FOR ADVERSE EVENTS PROSPECTIVELY IN FUTURE TRIALS.

AND FINALLY, IN THIS PROCESS OUR GOAL IS TO BALANCE RISKS THAT WILL VARY FROM TRIAL TO TRIAL, FROM DISEASE TO DISEASE AS NEW INFORMATION IS COLLECTED AND AS WE LOOK AT SPECIFIC MECHANISMS AND SPECIFIC CIRCUMSTANCES.

SO HOW DO WE DO ALL OF THESE THINGS? THERE ARE A COUPLE OF PIECES HERE. ONE IS THAT PUBLIC OUTREACH IS ESSENTIAL. I KNOW THAT THAT'S BEEN PART OF THE CONVERSATION FROM THE VERY BEGINNING OF PROPOSITION 71 IN THIS STATE, OUR DISCUSSIONS ABOUT STEM CELLS, THAT WE NEED TO HAVE THE PUBLIC UNDERSTAND WHAT THE SCIENCE IS AND WHERE WE'RE GOING. BUT THE NATURE OF THESE TRIALS AS WE'RE ENTERING THEM, THE NATURE OF WHAT WE'RE DOING MEANS THAT WE NEED PEOPLE TO UNDERSTAND WHAT IS STEM CELL RESEARCH AND WHAT ISN'T.

I THINK MOST PEOPLE IN THIS ROOM ARE AWARE THAT THERE'S A LOT THAT GOES ON NOW THAT IS LABELED AS STEM CELL RESEARCH AND HAS THAT CACHE OF BEING MAGIC AND GOLDEN WHEN, IN FACT, SOMETIMES IT IS BASED ON EXTREMELY POOR SCIENCE AND IS NOT EVEN STEM

CELLS IN THE SENSE OF THE KIND OF RESEARCH THAT MOST OF US ARE FOCUSED ON.

SECONDLY, EXISTING INSTITUTIONAL REVIEW COMMITTEES HAVE THE STRUCTURE AND THE EXPERTISE TO ADDRESS ALMOST EVERYTHING THAT I'VE JUST DESCRIBED. CERTAINLY THE EXPERTISE IS THERE, AND THE STRUCTURE COULD BE USED APPROPRIATELY TO MEET THE STANDARDS THAT WE'RE TALKING ABOUT. THE PROBLEM IS THAT THAT ISN'T LIKELY TO HAPPEN UNLESS THERE IS A SPECIFIC CHARGE TO THOSE COMMITTEES.

ONE WAY FOR THAT SPECIFIC CHARGE TO OCCUR IS THROUGH REGULATION, AND THAT'S A PLACE WHERE THE STATE OF CALIFORNIA MIGHT SAY THIS IS WHAT WE EXPECT YOU TO DO THAT IS EXTRA IN ORDER TO ADDRESS THESE ISSUES. AND THESE COMMITTEES ARE THE PLACES THAT MIGHT OCCUR.

THE OTHER WAY TO DO IT IS, AND I'M NOT A BIG FAN OF REGULATION, I JUST SEE THAT SOMETIMES THINGS DON'T HAPPEN WITHOUT REGULATION, ANOTHER WAY TO DO THIS IS BY CONSENSUS. TO BRING TOGETHER PEOPLE, AND BERNIE'S MENTIONED A CONSENSUS KIND OF A MEETING, STATEWIDE MEETINGS TO LOOK AT WHAT WE WANT TO DO. AND AS A COMMUNITY WE CAN DECIDE WHERE WE WANT TO SET THE STANDARDS AND SET GUIDELINES, AND IT WOULD BECOME SIMPLY ACCEPTED THAT THIS IS THE WAY

GOOD PRACTICE IS HANDLED. IT DOESN'T MEAN THAT EVERYBODY WILL HAVE TO DO IT, BUT MOST PEOPLE WOULD DO IT. AND IT MAY BE THE MOST EFFECTIVE WAY TO MOVE FORWARD.

SO THOSE ARE SOME THOUGHTS ON WHAT WE MIGHT DO, AND I THINK I WAS AS BRIEF AS ASKED TO BE, SO WE HAVE TIME FOR DISCUSSION.

CHAIRMAN LO: GREAT. THANKS VERY MUCH, MIKE. QUESTIONS, COMMENTS FOR DR. KALICHMAN?

DR. WAGNER: FIRST OFF, I THINK A NUMBER OF THE ISSUES THAT YOU ADDRESS, THERE'S A LOT OF DIFFERENT ISSUES TO ADDRESS SIMULTANEOUSLY. ONE THING I WOULD JUST SUGGEST FROM THE VERY BEGINNING IS THAT WE DO HAVE A STEM CELL THERAPY ALREADY THAT REALLY IS USED IN EVERY APPLICATION WHETHER IT BE NEUROLOGICAL DISEASE OR EVERY OTHER DISEASE, AND THAT IS BONE MARROW TRANSPLANT. RIGHT NOW IT IS THE ONLY PROVEN STEM CELL THERAPY THAT EXISTS AND HAS BEEN IN THE PROCESS FOR 40 YEARS.

SO THERE'S A LOT OF LESSONS TO BE GAINED BY GOING BACK AND LOOKING AT SOME OF THOSE WHETHER IT BE CONSENT PROCESS OR WHETHER IT BE THE ANIMAL STUDIES THAT HAVE BEEN PERFORMED PRIOR TO MOVING FORWARD TO THESE THERAPIES.

BUT I THINK THAT WHAT'S DIFFERENT ABOUT

BONE MARROW TRANSPLANTS TYPICALLY, THAT IS CLASSIC BONE MARROW TRANSPLANTS TYPICALLY, AND THIS NEW STEM CELL THERAPEUTICS THAT ARE BEING SUGGESTED IN THE PRESS, AND THAT IS IT'S REALLY THE PATIENT POPULATION FOR WHICH YOU'RE DOING THE TREATMENT FOR. AND AS YOU SAY, HIGHLIGHTING THESE FIRST THERAPIES, PARTICULARLY FOR VERY ADVANCED HIGH RISK PATIENTS WITH END STAGE OR WITH VARIOUS SEVERE DISEASES, HOWEVER THAT'S DEFINED, IS PROBABLY PART OF THE PROBLEM THAT WE'VE GOTTEN INTO WHERE WE'VE BEEN TALKING ABOUT THINGS LIKE DIABETES AND THINGS LIKE SPINAL CORD INJURY, WHICH MAY NOT BE THE SAME CHARACTER AS PATIENTS WITH PANCREATIC CANCER AS A FIRST SORT OF FIRST-IN-MAN TYPE OF THERAPY.

SO ONE THING I DON'T WANT TO FORGET, THOUGH, AND THAT IS THAT WHEN WE TALK ABOUT A NUMBER OF THE ISSUES, HOW WE REGULATE THE FIELD OR HOW WE SET STANDARDS FOR STEM CELL THERAPIES, REMEMBER WE DO HAVE LESSONS FROM BONE MARROW TRANSPLANT WHICH IS THE ONLY IRREVERSIBLE THERAPY THAT WE'VE EVER DONE, AND IT IS VERY POSSIBLE THAT ES CELLS WILL NOT BE IRREVERSIBLE BECAUSE OF THE FACT THAT THEY'RE IMMUNOLOGICALLY DIFFERENT FROM THE PATIENT FOR WHOM THEY'RE INTENDED TO BE TREATED.

SO AGAIN, I WOULD GO BACK TO BONE MARROW

TRANSPLANTING, BEGIN THERE WITH SOME OF YOUR COMMENTS.

DR. KALICHMAN: THAT'S ACTUALLY AN EXCELLENT POINT, AND I DIDN'T MEAN TO IMPLY THAT WE HAVEN'T DONE THINGS THAT ARE IRREVERSIBLE BEFORE. AND WE HAVE DONE OTHER THINGS THAT ARE IRREVERSIBLE AS WELL. THERE ARE A VARIETY OF SURGERY, SURGICAL TREATMENTS IN THE FIELD THAT I WAS INVOLVED WITH FOR QUITE A WHILE IS EPILEPSY. AND THE IDEA OF GOING INTO THE BRAIN AND CUTTING THE CORPUS CALLOSUM TO SEPARATE THE TWO HEMISPHERES, THAT WAS IRREVERSIBLE. YOU COULDN'T DECIDE LATER I WANT MY HEMISPHERES CONNECTED BACK UP AGAIN.

SO, YES, WE DO HAVE PLENTY OF EXPERIENCE, BUT WHAT WE HAVE RIGHT NOW IS THIS USUALLY BOLD LINE BETWEEN PREPLURIPOTENT STEM CELL RESEARCH AND POST WHERE WE ARE NOW PUTTING CELLS INTO THE BODY THAT COULD BECOME ANY CELL OF THE BODY; OR IF WE DIFFERENTIATED THOSE CELLS, THERE'S A LOT OF INTEREST IN PUTTING THOSE CELLS INTO THE BRAIN, WHICH RAISES A WHOLE NEW LEVEL OF CONCERN BECAUSE MOST OF US THINK OF THE BRAIN AS BEING THE CENTER OF WHO WE ARE. AND SO THOSE IRREVERSIBLE CHANGES MAY BE CONSIDERED EVEN MORE DRAMATIC AND WORRISOME THAN SOME OF THE OTHERS THAT WE MIGHT SEE. BUT THERE'S A

LOT TO BE LEARNED FROM THE OTHER.

DR. PRIETO: THIS IS OBVIOUSLY MAKING US ALL THINK A LOT ABOUT THIS. I THINK ONE OF OUR CHARGES AT THE CIRM IS TO IDENTIFY POSSIBLE CLINICAL APPLICATIONS FOR THIS RESEARCH AND HELP MOVE THEM INTO THE CLINIC. AND SO I THINK THE IDEA THAT BERNIE PROPOSED OF SCREENING OR HELPING TO CONVENE A CONSENSUS CONFERENCE THAT WOULD IDENTIFY THOSE POINTS THAT ARE GETTING IN THE WAY, INCLUDING THESE ISSUES, SEEMS LIKE A VERY GOOD IDEA TO ME.

CHAIRMAN LO: SHERRY.

MS. LANSING: I WANT TO THANK YOU FOR YOUR REPORT, AND WHAT WAS PARTICULARLY ENCOURAGING TO ME AS A PATIENT ADVOCATE, THAT SO MUCH OF WHAT YOU'RE RECOMMENDING ARE THE ISSUES THAT BERNIE AND OUR GROUP WAS ALSO BRINGING. AND I THINK THAT'S GREAT THAT THERE WAS REPETITION BECAUSE REPRESENTING THE PUBLIC, WHICH IS WHAT THIS, YOU KNOW, PROP 71 DOES, I THINK THAT WE HAVE AN OBLIGATION. I DON'T WANT TO SAY TO DO IT BETTER, BUT TO LOOK AT THE WAY IT'S BEEN DONE AND TO REEVALUATE IT AND TO MAKE SURE IT'S THE BEST WAY THAT IT'S BEEN DONE AND TO MAKE SURE THAT IT ADVANCES IT IN THE SAFEST POSSIBLE WAY.

AND WHEN WE DID THIS WITH THE OOCYTE DONATIONS, WE ACTUALLY CONSCIOUSLY SAID WE WERE

GOING TO ERR ON THE SIDE OF CAUTION AND WE COULD ALWAYS PULL BACK. AND I GUESS THAT'S REALLY WHAT I WOULD LIKE US TO DO. DO YOU KNOW? BECAUSE WE'RE GOING INTO UNCHARTERED TERRITORY. THERE HAS BEEN A LOT OF CONTROVERSY WITH IT. I WANT US TO ADVANCE AS QUICKLY AS POSSIBLE, BUT ERR ON THE SIDE OF CAUTION BECAUSE WE CAN ALWAYS PULL SOMETHING BACK.

I THINK A CONFERENCE TO GATHER COLLABORATION IS A MUST. AND I THINK DISSEMINATING INFORMATION WHICH I KNOW IS CONTROVERSIAL IS ALSO PART OF THE CHARTER THAT WE ADOPTED. I MEAN WE ACTUALLY SAID THAT ANYONE THAT FUNDED -- GOT FUNDING FROM US WOULD HAVE TO DISSEMINATE ALL THE INFORMATION. SO THIS IS REALLY AN EXTENSION OF THAT. AND OUR GOAL IS TO GET COLLABORATION BECAUSE THAT'S THE ONLY WAY THAT WE'RE GOING TO ADVANCE THINGS FURTHER.

AND THEN, YOU KNOW, TO LOOK AT SOME OF THE PRACTICES THAT ARE CURRENTLY DOING AND SAYING ARE THESE THE MOST ETHICAL. AND AS BERNIE SAID, IS THIS THE ONLY WAY? DO YOU HAVE TO DO THE SURGERY? DO YOU GIVE A PILL AND TELL PEOPLE THAT THIS PILL IS GOING TO WORK? AND DO THEY THEN HAVE THE MIND-SET THAT ENCOURAGES THEM TO HEAL PERHAPS.

SO I'M VERY GRATEFUL FOR YOUR REPORT, AND

I'M ALSO VERY GRATEFUL THAT ALL OF US ARE KIND OF THINKING THE SAME WAY.

DR. KALICHMAN: I WOULD HESITATE TO ADD ANYTHING TO THAT BECAUSE I APPRECIATE WHAT YOU SAID. BUT I WOULD GO ONE STEP BEYOND YOUR POINT THAT THERE'S AN OBLIGATION TO DO THIS WELL BASED ON CALIFORNIA'S CONFIDENCE IN TRYING TO MOVE THIS MISSION FORWARD. I LOOK AT IT AS AN OPPORTUNITY, AND IT'S AN OPPORTUNITY TO DO SOMETHING BETTER THAN WE'VE DONE IN THE PAST. AGAIN, THERE'S THAT BOLD LINE OF A NEW KIND OF RESEARCH AND NEW APPROACH THAT AT LEAST IN SAN DIEGO WE'RE SEEING SOME EXAMPLES OF THE WAYS WE'RE DEALING WITH THIS RESEARCH DIFFERENTLY THAN WE DEALT WITH OTHER RESEARCH TO BE SURE THAT IT'S DONE AS WELL AS POSSIBLE.

MS. LANSING: THANK YOU.

CHAIRMAN LO: ROB.

DR. TAYLOR: THAT WAS, THANKS, I THINK A REALLY REASONED AND NICE PRESENTATION. AND I'D LIKE TO ACTUALLY COME BACK TO YOUR POINT NO. 7 AND MAYBE PARAPHRASE THAT A LITTLE BIT BECAUSE I THINK THE CONCEPT DOWN BELOW IT IS REALLY CRITICAL HERE. AND I DO BELIEVE THAT WE'RE TALKING ABOUT SETTING STANDARDS THAT ARE HIGHER THAN WHAT'S OCCURRED IN THE PAST. AND I'M NOT CONVINCED THAT THAT'S WHAT'S

GOING FORWARD PRESENTLY.

SO AS YOU SAY, THIS IS A VERY CONTROVERSIAL AREA. I THINK THAT WHAT WE NEED TO DO IS HAVE THE CONSENSUS THOUGHT LEADERS THAT BERNIE HAS SUGGESTED, BUT WE REALLY NEED TO BRING THE FDA IN TO INFORM THEM BECAUSE, FROM WHERE I'M SITTING, THE LEAST AMOUNT OF INFORMATION MIGHT BE RESTING WITH THAT GROUP. AND WE MIGHT BE IN A POSITION WHERE WE CAN ACTUALLY INFORM THEM OF WHAT SHOULD GO FORWARD AS OPPOSED TO HAVING THE CART BEFORE THE HORSE, I THINK.

CHAIRMAN LO: JEFF.

MR. SHEEHY: I JUST HAVE A QUESTION. WHAT IS THE SPECTRUM OF CELL THERAPY THAT WE'RE TALKING ABOUT HERE? AND I GUESS FROM DR. WAGNER'S COMMENTS ABOUT BONE MARROW TRANSPLANTS WHICH ARE OCCURRING RIGHT NOW, PRESS REPORTS OF FETAL TISSUE TUMOR THAT WAS PUBLISHED IN *PLOS* FROM A FETAL STEM CELL TRANSPLANT THAT HAPPENED, ARE WE JUST TALKING ABOUT ES CELLS? BECAUSE WE HAVE ES CELLS, WE'LL HAVE IPS CELLS, WHAT ARE OUR BOUNDARIES HERE? AND SOME OF IT SEEMS TO BE PROCEEDING, YOU KNOW, KIND OF HELTER-SKELTER. THE ADULT STEM CELL FIELD SEEMS TO BE MOVING FORWARD. WHERE IS OUR CIRCLE?

DR. KALICHMAN: I THINK THERE ARE AT LEAST

SEVERAL KINDS OF ANSWERS TO THAT. ONE IS A REGULATORY ANSWER, WHICH IS WHAT IS GOING TO BE IN THE PURVIEW OF CIRM AND PURVIEW OF OUR SCRO AND ESCRO COMMITTEES. AND I'M NOT GOING TO ANSWER THAT QUESTION. I'LL LET OTHERS FROM CIRM ANSWER HOW THEY SEE THAT PLAYING OUT.

BUT THE OTHER QUESTION IS SORT OF A SOCIAL/ETHICAL QUESTION, AND THAT'S WHAT IS PLAYING OUT IN THE MINDS OF THE PUBLIC WHEN THEY HEAR THE WORD "STEM CELLS"? AND THE WORD "STEM CELLS" WERE HERE WELL BEFORE PROP 71. AND WE'VE HAD THIS SENSE OF STEM CELLS FOR MANY YEARS, AND YET NOW ALL OF THESE DIFFERENT KINDS OF CELLS ARE CLASSIFIED IN THE SAME WAY.

AND IN SAN DIEGO WE HAD A CONSIDERABLE AMOUNT OF DISCUSSION ABOUT PEOPLE WHO HAVE BEEN WORKING IN THE BONE MARROW STEM CELL AREA, HEMATOPOETIC STEM CELL FIELD FOR A LONG TIME, AND SEEING SOME PEOPLE IN THOSE FIELDS MOVING FORWARD WITH CLINICAL TRIALS THAT ARE PROMISING PERHAPS MORE THAN YOU WOULD EXPECT. THAT DOESN'T MEAN THEY'RE WRONG, BUT IT MEANS THAT THEY'RE PROMISING A GREAT DEAL. AND THEN IF YOU'RE A MEMBER OF THE PUBLIC THINKING ABOUT ENTERING A CLINICAL TRIAL, YOU HEAR STEM CELLS AND YOU HEAR ALL THE HYPE ABOUT STEM

CELLS DOING EVERYTHING, YOU'RE MORE LIKELY TO ENTER THAT TRIAL AND NOT CONSIDER THE RISKS. THAT'S JUST WITHIN THE REGULATORY STRUCTURE OF THE UNITED STATES. BUT ALL YOU HAVE TO DO IS CROSS THE BORDER, THEN, INTO TIJUANA, HEAR ABOUT THINGS GOING ON IN CHINA WHERE PEOPLE ARE GOING AND GETTING SO-CALLED STEM CELL THERAPIES WHERE THEY'RE PROMISING THINGS THAT THOSE OF US WHO UNDERSTAND SCIENCE AND THE NERVOUS SYSTEM, FOR EXAMPLE, FIND UNCONSCIONABLE BECAUSE THEY'RE PROMISING THINGS THAT ARE IN ALL LIKELIHOOD IMPOSSIBLE AS FAR AS WE CAN TELL AND YET CHARGING PEOPLE MONEY FOR BEING PARTS OF WHAT ARE SO-CALLED TRIALS.

SO WHEN YOU SAY WHAT'S THE SPECTRUM, FOR ME IT'S ANYTHING THAT ENDS UP HAVING THAT WORD "STEM CELL" IN IT IS SOMETHING WE SHOULD BE THINKING ABOUT WHEN WE TALK ABOUT THE ETHICAL ISSUES.

MR. SHEEHY: AND WE CAN ACTUALLY FUND, I BELIEVE, THE WHOLE SPECTRUM, SO --

DR. KALICHMAN: WELL, NOT THE BAD STUFF. YOU'RE NOT GOING TO FUND THE BAD STUFF.

DR. PRIETO: MAYBE WE HAVE TO HELP DETERMINE WHAT THE BAD STUFF IS.

DR. CSETE: I THINK THAT I REALLY WANT TO CORRECT SOMETHING ABOUT FDA NOT HAVING THE

EXPERIENCE AND THE VIEW OF ALL OF THIS. THEY SEE AN ENORMOUS AMOUNT MORE THAN WE WILL SEE ACROSS OUR DESKS. AND THERE'S -- AND THAT'S WHY IT'S VERY IMPORTANT FOR US TO SORT OF HAVE AN ONGOING DIALOGUE WITH THEM SO THAT WE CAN TRANSMIT BACK TO OUR INVESTIGATORS INFORMATION THAT'S NOT CONFIDENTIAL THAT WE LEARN FROM HAVING THAT ONGOING DIALOGUE.

AND E. J. IS PART OF A STANDING COMMITTEE AT FDA, AND I THINK YOU WANT TO SAY -- YOU SHOULD SAY SOMETHING ABOUT THE SPECTRUM OF THINGS THAT COME BEFORE THEM.

DR. READ: YOU MEAN FOR THE LIAISON COMMITTEE. SO, YEAH, I'M ON A CELL THERAPY LIAISON COMMITTEE WITH FDA. AND FDA ACTUALLY HAS LIAISON COMMITTEES IN ALL DIFFERENT AREAS, BLOOD AND, YOU KNOW, DRUGS, VARIOUS OTHER THINGS. AND THAT LIAISON COMMITTEE ACTUALLY HAS REPRESENTATIVES FROM A NUMBER OF STAKEHOLDER ORGANIZATIONS. AND ACTUALLY MARIE WAS TRYING TO GET CIRM TO BE A STAKEHOLDER ORGANIZATION, AND I THINK THAT'S A WORK IN PROGRESS BECAUSE IT'S A STATE ORGANIZATION, AND THEY WEREN'T INITIALLY WILLING TO TAKE ON STATE ORGANIZATIONS, BUT WE'RE LOBBYING A LITTLE BIT THERE.

SO I'M REPRESENTING ONE OF THE OTHER ORGANIZATIONS. AND THAT LIAISON MEETING IS A FORUM

FOR STAKEHOLDERS TO EDUCATE FDA ABOUT WHAT'S GOING ON. AND SOMETIMES THEY COMMENT AND SOMETIMES THEY DON'T, BUT THAT'S ONE OF THE MECHANISMS TO HAVE AN ONGOING DIALOGUE WITH THEM.

THE OTHER MECHANISM IS THAT THERE ARE MEETINGS OF PROFESSIONAL ORGANIZATIONS. SO, FOR EXAMPLE, WE'VE HAD THIS SOMATIC CELL THERAPY MEETING FOR THE LAST NINE YEARS THAT HAS ACTUALLY BEEN CO-SPONSORED BY FDA, ALTHOUGH THE CO-SPONSORSHIP IS PROBABLY GOING TO GO AWAY, WHICH ISN'T THAT BIG A DEAL. BUT AT THAT MEETING WE HAVE TRIED TO ACTUALLY PRESENT CASES OF NEW THERAPIES BEING DEVELOPED GOING INTO CLINICAL TRIALS, PRECLINICAL DATA, QUALITY ISSUES, AND SO ON. AND FDA HAS ACTUALLY BEEN A WILLING PARTICIPANT IN THAT. SO THAT'S BEEN A GOOD MECHANISM FOR DIALOGUE.

THE KEY ISSUE IS THAT THEY'RE NOT ALLOWED TO TELL YOU WHAT INDIVIDUAL SPONSORS HAVE DONE. SO THE KEY IS TO TRY TO GET THE SPONSORS TO GET OUT AND GET AWAY FROM THIS PROPRIETARY THING AND SHARE THAT WITH OTHER PEOPLE. AND I THINK TO THE EXTENT THAT CIRM CAN ENCOURAGE THAT, THAT'S GOING TO BE REALLY VALUABLE. BUT I AGREE WITH MARIE. FDA ACTUALLY KNOWS A WHOLE LOT MORE THAN -- THEY JUST CAN'T COMMUNICATE IT.

DR. TAYLOR: THAT'S REASSURING. I GUESS THE LACK OF TRANSPARENCY, THERE IS A GOOD SIDE OF THAT, THAT THE INFORMATION REALLY IS GOING IN, BUT IT'S KIND OF HARD FOR US OUTSIDE OF THAT SYSTEM TO REALLY BE ABLE TO UNDERSTAND THAT.

DR. READ: BUT I THINK THE BIG EFFORT SHOULD BE TO TRY TO KEEP ENGAGING THEM. AND SO THAT'S WHERE WE'RE TRYING TO HAVE THIS MEETING IN MAY TO REALLY GET THAT GOING BECAUSE I THINK THAT COULD BE AN ANNUAL MEETING. IT COULD GROW. BUT THE REAL KEY THERE IS TO GET SPEAKERS WHO, EVEN FROM COMPANIES, WHO ARE WILLING TO SAY HOW THEY PUT TOGETHER THEIR PRECLINICAL SAFETY PROGRAM AND WHAT FDA SAID ABOUT IT. BECAUSE FDA CAN'T GET UP AND SAY, WELL, THIS IS WHAT WE SAID ABOUT IT BECAUSE THAT'S PROPRIETARY.

CHAIRMAN LO: COULD I ASK ELIZABETH AND MARIE A FOLLOW-UP QUESTION? SO WHAT ARE THE INCENTIVES THAT WOULD ENCOURAGE SPONSORS TO VOLUNTARILY DISCLOSE INFORMATION THAT THE FDA IS CHARGED WITH KEEPING CONFIDENTIAL? AND WHAT KIND OF -- WHAT'S IN THE TOOLBOX THAT CIRM HAS AT ITS DISPOSAL TO SORT OF ENCOURAGE MORE TRANSPARENT DISCUSSION OF THOSE CONFIDENTIAL MATERIALS?

DR. CSETE: WE CAN ENCOURAGE. I THINK

THAT'S THE RIGHT WORD. I THINK LOOKING AT THE PUBLICATION BEHAVIOR OF SOME OF THE COMPANIES THAT ARE FAR ALONG IN THIS IS INTERESTING. I THINK NOVOCELL, FOR EXAMPLE, HAS BEEN VERY OPEN ABOUT PUBLISHING DETAILS OF ITS PROTOCOLS, HIS DIFFERENTIATION PROTOCOLS, TO GET TO BETA CELLS; WHEREAS, WE HAVEN'T FROM OTHER COMPANIES SEEN THAT KIND OF DETAIL. AND THE COMPANY'S COMFORT LEVEL WITH THAT INFORMATION IS SOMETHING WE JUST, YOU KNOW, CAN'T CONTROL.

DR. READ: I AGREE. I'M ALWAYS BEWILDERED BY -- I DON'T KNOW HOW THEY MAKE THAT DECISION. I MEAN THEY HAVE INTERNAL DECISIONS IN THE COMPANIES, AND I HAVEN'T BEEN -- YOU CAN'T PREDICT WHO'S GOING TO DO IT AND WHO'S NOT. WHEN WE CHOSE SOME SPEAKERS FOR THIS MAY MEETING, I HAD TO KIND OF GO BEHIND THE SCENES TO SOME PEOPLE I KNOW AND SAY WHO DO YOU THINK WILL DO IT. AND THEY SAY I THINK THIS PERSON, YOU KNOW, BECAUSE THERE'S A LOT OF BEHIND THE SCENES KNOWING WHO WILL BE ABLE TO SPEAK AND NOT. AND THEN THEY HAVE TO KIND OF GET A CORPORATE DECISION.

WE'VE BEEN IN THE POSITION WHERE WE'VE INVITED SPEAKERS AND WE THOUGHT THEY WERE GOING TO SAY SOMETHING, AND THEY SHOW UP AND THEY SAY A CERTAIN AMOUNT, BUT SOMEBODY IN THE RISK MANAGEMENT

OR SOMEWHERE ELSE IN THEIR CORPORATION CUTS IT OFF AT SOME POINT. SO, YOU KNOW, IT'S HARD TO PREDICT. I WOULD SAY AS A GENERAL STATEMENT THE ACADEMIC PEOPLE ARE ALWAYS MORE WILLING TO REVEAL WHAT THEY'RE DOING.

DR. CSETE: AND I WOULD -- I'M REALLY HAPPY FOR SUGGESTIONS, BUT I THINK FROM OUR PERSPECTIVE, WE NEED SOMETHING REALLY QUITE CONCRETE. WHAT CAN WE DO -- YOU KEEP TALKING ABOUT BEYOND THE FDA, BEYOND THE OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTION, BEYOND, BEYOND. AND THOSE -- A LOT OF THESE THINGS ARE GOING TO BE -- AND BEYOND THE FACT THAT WE WILL HAVE AN ACTIVE PRESENCE ON MONITORING BOARDS FOR DISEASE TEAMS, WE CAN'T REGULATE. WE CAN ENCOURAGE. AND I THINK WE CAN CERTAINLY DEVELOP A FORUM FOR NEGATIVE DATA. WE'RE NOT TALKING ABOUT TRIALS AT THIS POINT BECAUSE WE'RE NOT FUNDING TRIALS, BUT NEGATIVE DATA THAT IS IMPORTANT FOR PEOPLE TO SEE WHICH IS DIFFICULT TO PUBLISH.

SO YOU CAN TRY TO ENFORCE PUBLISHING, FOR EXAMPLE, BUT FINDING A PUBLISHER WHO WILL TAKE NEGATIVE DATA ISN'T ALWAYS TRIVIAL. SO I THINK -- AND WE HAVE TALKED INTERNALLY ABOUT USING OUR WEBSITE AND OUR GRANTEES MEETINGS AND OTHER

MECHANISMS FOR GETTING THAT KIND OF DATA ACROSS. BUT BEYOND WHAT'S THERE ALREADY TO PROTECT PATIENTS AND PUTTING UP BEAUTIFUL -- THE BEST POSSIBLE CONSENT FORMS, THE BEST POSSIBLE EXAMPLES OF RESEARCH, WE NEED SOME HELP ABOUT WHAT THAT EXACTLY MEANS.

CHAIRMAN LO: PAT AND THEN --

DR. OLSON: I JUST WANT -- THIS IS A VERY DIFFICULT QUESTION. AND COMING FROM AN INDUSTRY VIEWPOINT, I GUESS I JUST WANT TO -- OR COMING FROM HAVING BEEN IN INDUSTRY, I GUESS, I MEAN I THINK NOVOCELL HAS BEEN ONE OF THE MORE OPEN ABOUT IT. IT MAY BE BECAUSE THEY FEEL THEY'RE VERY SECURE IN THEIR PROPRIETARY POSITION. OTHER COMPANIES WHO MAY HAVE PATENTS THAT ARE MORE PATENTS AS OPPOSED TO COMPOSITION OR GOING TO NEED TO LICENSE PATENTS, THEY HAVE TO PROBABLY -- THEY HAVE TO MAINTAIN WHAT I'LL CALL TRADE SECRETS AND/OR INTELLECTUAL PROPERTY TO PUT THEM IN A POSITION TO ALMOST BE ABLE TO ACQUIRE IN SOME CASES WHAT THEY MAY NEED OR TO TRADE.

IT'S NOT -- I'VE HEARD OF COMPANIES WHO HAVE GONE OUT OF BUSINESS BECAUSE THEY WERE NOT ABLE TO GET A KEY PIECE OF INTELLECTUAL PROPERTY EVEN THOUGH THEY'VE HAD A LOT OF PROCESS PATENTS AROUND

IT. I THINK A LOT OF THE TIMES COMPANIES VIEW SOME OF THIS INFORMATION AS COMPETITIVE ADVANTAGE. SO IT'S A VERY DIFFICULT SITUATION. I THINK I'M EVEN CONCERNED IN APPLICATIONS WE GET FROM COMPANIES AS WE GO FORWARD WHEN WE ASK THEM TO DESCRIBE THEIR PRECLINICAL PACKAGE OR THEIR REGULATORY STRATEGY OR WHEN WE HAVE -- HOW ARE WE -- WHAT KIND OF INFORMATION ARE WE GOING TO GET AND WHAT KIND OF BOUNDARIES ARE THEY GOING TO PUT ON US FOR DISCLOSURE? BECAUSE IT'S THE SAME SORT OF THING, WHEREAS I DO APPRECIATE THE DESIRE TO TRY AND HAVE THIS AS TRANSPARENT AS POSSIBLE.

AND ANOTHER THING THAT IN SOME SENSES PUT THIS IN PERSPECTIVE FOR ME. WHEN I TALKED TO THE FDA HEAD FOR SELLING GENE THERAPY, AND THEY SAID THAT THE NUMBER OF ACTIVE IND'S, 70 PERCENT OF THOSE WERE FROM ACADEMIC INVESTIGATORS. VERY FEW ARE FROM COMPANIES WHO ARE THE PEOPLE WHO ARE ACTUALLY TAKING THINGS FORWARD TO MARKET. AND THE MAJORITY OF THE ACADEMIC INVESTIGATORS ARE THOSE WHO ARE -- I MEAN I THINK IT'S ACKNOWLEDGED. THEY'RE ANSWERING AN IMPORTANT QUESTION WHICH WE HOPE WILL ADD TO THE KNOWLEDGE BASE THAT WILL MOVE THE FIELD FORWARD BROADLY. BUT THEY'RE GENERALLY NOT ON A COMMERCIALIZATION TRACK. SO IT'S A WHOLE DIFFERENT

THING WHEN YOU'RE ON A COMMERCIALIZATION TRACK. AND I JUST THINK YOU HAVE TO BALANCE ALL THESE KINDS OF FACTORS IN YOUR THINKING ABOUT THIS.

DR. KIESSLING: ONE OF THE THINGS THAT I'VE BECOME AWARE OF THAT I DIDN'T REALIZE BEFORE IS THAT A COMPANY CAN ORGANIZE A CLINICAL TRIAL THROUGH A HOSPITAL. IT CAN GO THROUGH THIS HUMAN SUBJECTS REVIEW PROCESS, AND THEN THE COMPANY OWNS THE DATA. SO FREQUENTLY THAT DATA IS NEVER DISCLOSED TO ANYBODY IF THEY CHOOSE TO NOT DISCLOSE IT. I DON'T KNOW WHAT WE CAN DO ABOUT THAT AS A COMMITTEE, BUT THAT'S ACTUALLY EVIDENTLY NOT A TRIVIAL PROBLEM. SO THAT PUTS THE INSTITUTION INTO THE POSITION OF WHERE THEY'VE RECRUITED HUMAN SUBJECTS TO PARTICIPATE IN THE RESEARCH, AND THE RESEARCH THEN IS NEVER REALLY DISCLOSED, WHETHER IT WORKED OR DIDN'T WORK OR WHATEVER.

AND I DON'T KNOW IF THAT'S SOMETHING THAT COULD BE DONE AT THE LEVEL OF THE STATE BECAUSE WE COULD ONLY, I'M ASSUMING, REGULATE FOLKS THAT REQUIRE CIRM FUNDS TO DO THEIR WORK. BUT THERE SEEMS TO BE SOMETHING REALLY WRONG WITH RECRUITING PEOPLE INTO ANY KIND OF HUMAN SUBJECTS RESEARCH AND THEN NOT HAVING THE INFORMATION KNOWN AFTER THAT.

CHAIRMAN LO: I HAVE ALTA AND THEN

FRANCISCO.

DR. READ: I WAS GOING TO MENTION THE ISSUE OF THE OWNERSHIP OF THE DATA. IN CLINICAL RESEARCH, THERE ARE SOME INSTITUTIONS -- WHEN I WAS AT THE NIH CLINICAL CENTER, THE NIH ALWAYS NEGOTIATED THAT THE NIH OWNED THE DATA. SO THIS IS IN THE INTRAMURAL PROGRAM. OKAY. SO IN OTHER WORDS, THAT WAS JUST PART OF THE AGREEMENT, THE LEGAL AGREEMENT.

DR. PRIETO: CASE BY CASE.

DR. READ: IT WAS DONE CASE BY CASE, I BELIEVE, BUT THAT'S HOW IT ALWAYS ENDED UP. BUT I DON'T KNOW WHAT OTHER UNIVERSITIES DO. AND THE THING IS THAT IF THEY GO IN --

MR. SHESTACK: THESE AREN'T (INDISCERNIBLE) IN THE INTRAMURAL PROGRAM.

DR. READ: RIGHT.

DR. OLSON: IT WON'T HAPPEN IN A COMPANY.

DR. READ: IN THE INTRAMURAL PROGRAM, THAT'S HOW IT ALWAYS KIND OF WORKED OUT. SO THAT'S WHAT WE WOULD HAVE. NOW, I DON'T KNOW WHAT DIFFERENT UNIVERSITIES DO. I DON'T KNOW WHETHER UCSF ARGUE THAT IS IT'S THEIR DATA, BUT I THINK YOU'RE RAISING A GOOD POINT. AND THE QUESTION IS IF CIRM IS GIVING MONEY TOWARDS A CLINICAL TRIAL, CAN

THEY SOMEHOW HAVE INFLUENCE OVER WHO OWNS THE DATA?

DR. KIESSLING: MY POINT IS NOT WHO OWNS THE DATA. MY POINT IS WHO KNOWS THE DATA? AND I THINK THERE'S REAL INTELLECTUAL PROPERTY ISSUES AROUND WHO OWNS THE DATA AND CAN PROTECT THE DATA. BUT I THINK THE ISSUE IS HOW CAN YOU PROMOTE AN ENVIRONMENT WHERE NO MATTER WHAT THE OUTCOME FROM THIS HUMAN SUBJECTS PARTICIPATION WAS, IT BECOMES PUBLICLY KNOWN.

CHAIRMAN LO: LET ME JUST ADD A FACTUAL STATEMENT. AT UCSF YOU CANNOT SIGN A RESEARCH CONTRACT OR GRANT UNLESS IN PART OF THE CONTRACT LANGUAGE THE INVESTIGATOR HAS THE RIGHT TO PUBLISH THE DATA WITHOUT CENSORSHIP, BUT THE SPONSOR HAS THE RIGHT TO DELAY PUBLICATION FOR SEVERAL MONTHS TO ALLOW A PATENT TO BE FILED SO THAT THAT'S PART OF THE CONTRACTUAL ARRANGEMENT BETWEEN THE INSTITUTION RECEIVING THE FUNDING TO CARRY OUT A TRIAL AND THE SPONSOR.

SO I HAVE A LOT OF PEOPLE ON THE LIST, SO LET ME GO THROUGH.

MR. SHESTACK: IT'S NOT NECESSARILY THAT IMPORTANT, BUT IN A TIME OF DIMINISHING FINANCES, IT MIGHT BE MORE IMPORTANT, WHICH IS NOBODY FEELS ANY COMPUNCTION EVER TO PUBLISH NEGATIVE RESULTS,

COMPANIES OR RESEARCHERS. BUT IT MIGHT SAVE A LOT OF TIME, AND IT MIGHT BE SOMETHING THAT WE WOULD LIKE TO PUT A RECOMMENDATION TOWARDS.

CHAIRMAN LO: I HAVE ALTA AND THEN FRANCISCO. OTHERS WANT TO GET IN ON THIS.

DR. TROUNSON: BERNIE, THIS IS A VERY IMPORTANT POINT, I THINK, COLLECTIVELY FOR THE WHOLE COMMUNITY BECAUSE IF YOU'RE UNABLE TO GET ACCESS TO WHAT THE NEGATIVE RESULTS ARE, REALLY WHAT YOU ARE GOING TO DO IS ENCOURAGE PEOPLE TO GO OFFSHORE, OFFSITE TO WHERE THEY'RE ADVERTISING CLINICAL TRIALS FOR THE BENEFIT OF A WIDE RANGE OF DISEASES. WE HAVE TO GET A PERSPECTIVE HERE THAT REALLY SORT OF IS IN THE INTEREST OF THE COMMUNITY AS WELL. SO I THINK CIRM SHOULD TAKE A ROLE. IT WILL NEED TO BE AT A LEVEL THAT WE'RE ALLOWED TO LEGALLY AND APPROPRIATELY UNDER THE STATUTES AND WHAT WE CAN NEGOTIATE. BUT I SENSE THAT IF WE DON'T DO THIS, WE DON'T TAKE THIS LEADERSHIP POSITION, WE'RE ACTUALLY NOT DOING ANYBODY A FAVOR. IN FACT, I THINK WE COULD BE CAUSING A GREAT DEAL OF DAMAGE.

SO I THINK THAT PERSPECTIVE NEEDS TO BE ON BOARD FOR ALL OF US BECAUSE I THINK THIS IS EXACTLY WHAT YOUR COMMITTEE, BERNIE, IS SORT OF CHARGED AT LOOKING AT CLOSELY.

CHAIRMAN LO: ALTA.

DR. CHARO: TWO THOUGHTS, ONE OF WHICH FOLLOWS DIRECTLY ON WHAT YOU SAID, ALAN. I THINK JUST IN TERMS OF DISCUSSING THIS, AND IN GENERATING SUPPORT OR DEBATE AMONG PARTICULARLY POLITICAL COMMUNITIES, I THINK IT'S VALUABLE TO BE A LITTLE MORE PRECISE ABOUT THE DOWNSIDES OF THE SECRECY BECAUSE RIGHT NOW THERE'S BEEN A VERY SUCCESSFUL MOVEMENT TO OPEN UP DATA, INCLUDING NEGATIVE DATA, FROM CLINICAL TRIALS THROUGH CLINICALTRIALS.GOV. AND THE THEORY THERE WAS YOU DID NOT WANT ADDITIONAL HUMAN SUBJECTS TO BE ENROLLED AND PUT AT MEDICAL RISK IF WE ALREADY KNEW FROM ANOTHER TRIAL THAT IT WAS EITHER INEFFECTUAL OR TOXIC. AND THAT WAS AN EASIER ARGUMENT TO MAKE BECAUSE IT WAS ABOUT HUMAN SAFETY AND ACTUAL INDIVIDUALS WHO MIGHT BE ENROLLED.

WHAT WE'RE TALKING ABOUT NOW IS A STEP BEHIND THAT, RIGHT, WITH THE PRECLINICAL WORK WHICH IS REALLY ABOUT NOT DIRECTLY HURTING A HUMAN BEING BY ENROLLING THEM POINTLESSLY. IT'S ABOUT THE ENTIRE FIELD BEING HELD BACK. AND THIS IS WHY YESTERDAY I SAID THERE'S A LOT OF ECHO HERE OF THE SAME CONVERSATIONS AROUND PATENTS BECAUSE IT IS THIS POTENTIAL ABOUT WHAT REALLY DOES MOVE THE FIELD FORWARD. IS IT SECRECY TO INCENTIVIZE MORE PEOPLE

TO INVEST SO THAT, FRUSTRATING AS IT IS, IT ALL MOVES FORWARD MORE QUICKLY, OR IS IT TRANSPARENCY, OR IS IT SOME SWEET SPOT. AND THE PROBLEM IS NO EMPIRICAL DATA TO TELL YOU WHICH ONE IS GOING TO ACTUALLY WORK.

SO JUST AS A POINT OF DISCUSSION, I THINK IN PUBLIC DISCUSSION IT'S GOING TO BE IMPORTANT TO NOTE THAT WHAT WE'RE REALLY TALKING ABOUT IS INTERVENING IN THE CURRENT VERSION OF CAPITALISM AND INTELLECTUAL PROPERTY AND NOT HUMAN SAFETY DIRECTLY, ALTHOUGH CLEARLY IT HAS AN EFFECT DOWN THE LINE.

THE SECOND WAS JUST A QUESTION THAT CAME TO MIND AFTER PAT SPOKE ABOUT CIRM'S OWN PROCESS. BECAUSE IT DOES SOUND LIKE TO SOME EXTENT YOU HAVE A SIMILAR DILEMMA TO THE FDA TAKING PLACE INTERNALLY. THAT IS, YOU RECEIVE GRANT PROPOSALS, THEY SPELL OUT A RESEARCH PROTOCOL, A QUESTION, AND A PROPOSED WAY TO ANSWER IT, BUT YOU MAY HAVE SEEN OTHER PROTOCOLS FROM OTHER PROSPECTIVE GRANTEES THAT HAVE GIVEN YOUR PEER REVIEWERS SOME INSIGHT INTO WHAT WORKS OR DOESN'T WORK.

SO I WAS JUST CURIOUS HOW YOU ARE OR ANTICIPATE MANAGING THAT PROCESS WITHIN YOUR OWN PEER REVIEW PROCESS FOR GRANT MAKING BECAUSE THAT MIGHT BE AN INTERESTING WAY TO THINK ABOUT MODELING

WHAT IT IS THAT YOU WANT TO BE DONE ON A BROADER SCALE.

DR. TROUNSON: I THINK THEY'RE VERY IMPORTANT POINTS BOTH, BUT THE LATER ONE, YOU KNOW, THERE ARE PEOPLE ON THE BOARD HERE WHO HAVE EXPERIENCED THIS. JEFF AND JOSE, FOR EXAMPLE. SO THOSE PEOPLE WHO SIT THERE TIME AFTER TIME AFTER TIME PROBABLY EVEN BETTER THAN SOME OF THE REVIEWERS IN SEEING THE DOWNSIDE OF, SAY, SOME ANIMAL MODELS OR SOME APPROACHES THAT ARE BY THE REFEREE'S ASSESSMENT NOT CONSIDERED STATE-OF-THE-ART OR AS GOOD AS SHOULD BE. AND THERE'S AN ISSUE THERE ABOUT THAT INFORMATION IN OUR RECORDS THAT WE NEVER GO IN AND COLLATE, IF YOU LIKE.

AND I DON'T KNOW IF THAT COULD CAUSE ANY DAMAGES IF WE DID GO IN AND COLLATE THE ASSESSMENTS OF REVIEWERS IN THESE AREAS, BUT IT COULD BE VERY HELPFUL. FOR EXAMPLE, IN SOME MODELS, PARTICULARLY THE ARGUMENT, FOR EXAMPLE, WHETHER WE SHOULD BE DOING PRIMATE RESEARCH AS WELL.

DR. CHARO: PARTICULARLY IF YOU WERE DOING REVISE AND RESUBMIT AS A RESPONSE TO A PROSPECTIVE GRANTEE.

DR. TROUNSON: RIGHT. SO I KNOW AND THE STAFF KNOW THAT AT TIMES THE REVIEWERS WILL BE,

BECAUSE WE HAVE A RANGE OF REVIEWERS, THAT THEY'LL BE UNAWARE OF PREVIOUS CRITIQUE OF A CERTAIN AREA, AND WE MIGHT BRING THAT TO THEIR ATTENTION, PARTICULARLY IF THERE IS A PUBLICATION ON IT. SO I THINK RESIDENT IN OUR INFORMATION BASE ARE SOME THINGS WHICH ARE PROBABLY VERY IMPORTANT. AND WE HAVEN'T AT THIS STAGE TRIED TO TRAWL THAT OUT, BUT I SUSPECT IT MIGHT BE USEFUL IF WE COULD FIND THE TIME TO DO THAT BECAUSE IT COULD BE HELPFUL TO APPLICANTS AND THE WHOLE FIELD GOING FORWARD.

DR. PRIETO: A COUPLE COMMENTS. FIRST, I APPRECIATE, ALAN, WHAT YOU'RE SAYING BECAUSE I AGREE THAT I THINK WE CAN PLAY A LEADERSHIP ROLE, ALTHOUGH WE ARE RESTRICTED TO WHAT WE FUND AND WHAT HAPPENS WITHIN CALIFORNIA UNDER OUR PURVIEW. BUT IT SEEMS TO ME THAT CONVENING A CONSENSUS CONFERENCE OR PARTICIPATING IN THAT MIGHT HELP TO DEFINE FOR RESEARCHERS AND APPLICANTS EVERYWHERE WHAT THE GENERAL CONSENSUS IS OF THE BEST PRACTICE IN THIS AREA.

AND I APPRECIATE, PAT, WHAT YOU'RE SAYING, THAT THERE'S A VERY FINE LINE HERE THAT HAS TO BE WALKED. AND YOU KNOW WHAT I THINK WE NEED MORE HELP ARRIVING AT IS DETERMINING WHERE THAT LINE NEEDS TO BE DRAWN. WHAT DO WE TELL PEOPLE APPLYING, AND

HOPEFULLY THAT STANDARD WILL BE ONE THAT WILL BE ACCEPTED MORE GENERALLY SO THAT RESEARCHERS WILL KNOW THIS IS WHAT I CAN EXPECT AND THIS IS THE BEST WAY TO GO FORWARD. AND WE HAVE TO BE VERY SENSITIVE TO THE FACT THAT WE ONLY WANT WHAT WILL MOVE THE RESEARCH FORWARD MORE EXPEDITIOUSLY. WE DON'T WANT ANYTHING THAT WILL SLOW IT DOWN, AND SO THAT'S PART OF DRAWING THAT LINE, DETERMINING WHAT YOU REVEAL AND WHEN.

CHAIRMAN LO: JOHN.

DR. WAGNER: SO GOING BACK TO SOME OF THE DISCUSSION OF TALKING ABOUT WHAT CAN CIRM DO CONCRETELY. AND I THINK THAT, JUST TO SUMMARIZE A LITTLE BIT, IS THAT IF I THINK BACK ABOUT THE COMMENTS BEING MADE, I THINK THAT CERTAINLY HAVING A CONSENSUS CONFERENCE THAT DEMONSTRATES WHAT BEST PRACTICES ARE SOUNDS LIKE A PRETTY EASY ONE TO MOVE FORWARD. AND WHAT YOU WANT TO FOCUS ON, I CAN'T SAY, BUT CONSENSUS DOES SOUND ALWAYS GOOD.

HOWEVER, WHEN I THINK ABOUT WHAT ELSE COULD YOU FOCUS ON, WHAT YOU MIGHT PUT FUNDING TOWARDS THAT WOULD HAVE BROAD IMPACT. AND ONE THING I CAN THINK OF IS THAT WE CAN TALK ABOUT ANIMAL MODELS FOR TOXICOLOGY. THAT'S SOMETHING THAT IMPACTS EVERYONE. ALTHOUGH I WOULD LIKE TO INCLUDE

IN THAT ANIMAL MODELS WITH PROOF OF CONCEPT, THAT'S GOING TO BE MUCH MORE PROJECT SPECIFIC. AND SO THAT ONE IS GOING TO BE HARDER TO TACKLE, BUT THE TOXICOLOGY SHOULD BE BROAD.

THE OTHER THING THAT I SEE WE SHOULD ALSO FOCUS ON WHAT KIND OF GENETIC TESTS AND INFECTIOUS DISEASE TESTING SHOULD BE DONE. AGAIN, THAT'S BROAD IMPACT BECAUSE IT'S GOING TO AFFECT EVERY CELL POPULATION THAT WE'RE GOING TO DEAL WITH. AND WE HAVE ALREADY GOOD IDEAS AND THAT COULD BE PART OF COMING OUT OF A CONSENSUS CONFERENCE, BUT THEN THAT MIGHT LEAD TO RFP'S WITHIN THE CIRM NETWORK TO SPECIFICALLY ADDRESS THOSE BROAD IMPACTING TYPES OF THINGS ACROSS THE BOARD.

AND THEN LASTLY, I THINK I LIKE THE IDEA OF MAYBE EVEN FOCUSING A STUDY ON THE CONSENT PROCESS ITSELF. YOU KNOW, AS YOU SAY, THAT IN PART WHAT WE'RE DEALING WITH IS A LOT OF MISINFORMATION AND PURPOSEFUL MISINFORMATION IN THE COMMUNITY. AND WE CLEARLY HAVE TO IMPROVE UPON THE COMMUNICATIONS. WE HAD A DISCUSSION YESTERDAY ABOUT HAVING THESE SORT OF PUBLIC FORA TO DISCUSS WHAT ARE THE REASONABLE EXPECTATIONS FOR STEM CELL THERAPIES. BUT IN ADDITION, I THINK THERE WOULD BE A HIGHER LEVEL OF CONFIDENCE IN THE PROCESS IF WE SAID WE'RE

EVEN STUDYING HOW TO MAKE THE CONSENT PROCESS MORE APPROPRIATE.

YOU GAVE US A WHOLE LIST OF REASONS WHY THAT WOULD BE A GOOD THING. AND I THINK THAT NOT ONLY WILL BE SOMETHING EXTRAORDINARILY POSITIVE FOR THE PUBLIC WITHIN CALIFORNIA. IT HAS INTERNATIONAL, BUT AT LEAST NATIONAL IMPLICATIONS THAT WE HAVEN'T ADDRESSED PROBABLY FOR A FEW DECADES IN A VERY SYSTEMATICALLY SCIENTIFIC WAY.

DR. ROBERTS: I JUST WANTED TO PICK UP ON THE CONSENSUS CONFERENCE AND POINT OUT THAT THERE SEEMS LIKE THERE ARE A COUPLE THINGS THAT THAT CONFERENCE COULD DO. ONE IS TO COME UP WITH SOME CONSENSUS OF BEST PRACTICES IN TERMS OF THE PROTECTION OF HUMAN SUBJECTS IN CLINICAL TRIALS AND ALSO EDUCATING THE PUBLIC ABOUT WHAT TO EXPECT FROM STEM CELL RESEARCH. IT SEEMS LIKE A LOT OF -- A KEY ELEMENT OF CONSENT AND OTHER ISSUES WE'VE BEEN TALKING ABOUT, ETHICAL ISSUES RELATED TO CLINICAL TRIALS, IS THE PUBLIC'S UNDERSTANDING OF WHAT WILL COME OUT OF THESE TRIALS. IN OTHER WORDS, HUMAN SUBJECTS COME TO THIS WITH AN UNDERSTANDING ABOUT WHAT TO EXPECT FROM THE TRIALS THAT IS A CRITICAL COMPONENT OF THE CONSENT PROCESS.

BUT THEN THERE ALSO AT THIS CONSENSUS

CONFERENCE COULD BE A DISCUSSION ABOUT THE ISSUES OF PROPRIETARY INFORMATION AND SECRECY VERSUS TRANSPARENCY. IT SEEMS LIKE WE'RE AT A STATE NOW WHERE THE RESEARCHERS ARE CONCERNED ABOUT COMPETITIVE ADVANTAGE AND WHO'S GOING TO REVEAL MORE THAN OTHERS. AND MAYBE IF A DISCUSSION AMONG THE RESEARCHERS OF WHAT WOULD BE -- YOU DON'T THINK THAT WILL WORK, PAT. I DON'T KNOW. AT LEAST -- I UNDERSTAND THERE ARE COMMERCIAL CONSIDERATIONS THAT PERHAPS NONE OF US IS GOING TO BE ABLE TO OVERCOME THAT'S THE BOTTOM LINE OF ALL OF THIS, AND MAYBE IT'S HOPELESS. BUT AT LEAST I'M THINKING THAT AT LEAST GETTING THE RESEARCHERS TO DISCUSS WHAT THOSE ARE, THEY'RE BETTER ABLE TO TELL US THAN WE CAN FIGURE OUT WHAT ARE THE CONCERNS AND PERHAPS SOME KIND OF DISCUSSION AMONG THE SCIENTISTS THEMSELVES OF WHAT MIGHT BE A WAY TO ENCOURAGE MORE TRANSPARENCY WOULD BE MORE USEFUL THAN US TRYING TO FIGURE OUT INCENTIVES WITHOUT THEIR INPUT.

DR. CSETE: SO LET ME JUST RESPOND. AGAIN, THIS IS IN THE SPIRIT OF US INFORMING YOU OF WHAT WE ARE DOING --

DR. ROBERTS: YES.

DR. CSETE: -- SO THAT I CAN UNDERSTAND MORE WHAT THE BEYOND MEANS WHEN BERNIE SAYS BEYOND.

WE HAVE A CONFERENCE GRANT MECHANISM FOR DEVELOPING A CONSENSUS CONFERENCE THAT'S OUT THERE ALREADY. IN TERMS OF JOHN'S SUGGESTIONS ABOUT ANIMAL MODELS, WE DID HAVE A TOXICOLOGY WORKSHOP, EVALUATED THE STATE OF THE ART. WE ARE FUNDING SEVERAL GROUPS WHO ARE DEVELOPING EMBRYONIC STEM CELL-BASED CELLS THAT WILL BE, WE HOPE, BETTER TOXICOLOGY MODELS THAN ANIMALS THEMSELVES.

WE HAVE CALLED FOR IN SEVERAL OF OUR RECENT GRANTS NEW ANIMAL MODELS OF DISEASE, BUT THEY JUST DON'T HAPPEN. WE DIDN'T GET APPLICATIONS IN THAT AREA. I THINK IT'S JUST BECAUSE PEOPLE ARE USING WHAT'S OPTIMAL, AND VERY OFTEN THE NEW ANIMAL MODELS APPEAR AS A SPONTANEOUS MUTATION OR SOMETHING LIKE THAT, AND IT WAS VERY DIFFICULT FOR REVIEWERS -- FOR OUR APPLICANTS TO COME UP WITH A WAY TO DEVELOP NEW ANIMAL MODELS.

DR. WAGNER: EXCEPT THAT, JUST A COMMENT THOUGH, IS THAT PEOPLE ARE USING THEM ALL THE TIME. SO THEY MAY NOT HAVE COME UP WITH A NEW ANIMAL MODEL, BUT PEOPLE ALREADY HAVE TO BE USING ANIMAL MODELS FOR WHICH TO DEVELOP PROOF OF CONCEPT. SO THERE'S A DISCONNECT BECAUSE THEY'RE NOT COMING UP WITH -- IT SOUNDS LIKE THEY USE THEM, BUT THEY DON'T WANT TO SPEND THEIR TIME DEVELOPING SORT OF BEST

PRACTICE ANIMAL MODELS, SO TO SPEAK. SO THERE'S GOING TO BE -- THERE'S A DISCONNECT BETWEEN HAVING AN RFP AND NOT RESPONDING AND THE FACT THAT THE COMMUNITY USES THEM.

DR. CSETE: OKAY. SO WHAT'S YOUR SUGGESTION FOR WHAT WE SHOULD DO WITH THAT?

DR. WAGNER: ACTUALLY I'M JUST RESPONDING TO YOUR COMMENT THAT NO ONE RESPONDED. FIRST OFF, I THINK IT'S GREAT THAT YOU'VE TRIED, BUT I CAN'T TELL YOU EXACTLY BECAUSE I DON'T KNOW HOW THE RFP WAS WORDED. IS THERE SOMETHING THAT WAS NOT COMMUNICATED OR NOT DESIRED, OR WHY IS IT THAT PEOPLE AREN'T RESPONDING? BUT THAT'S -- THAT'S PROBABLY A TOPIC FOR A DIFFERENT CONVERSATION.

DR. CSETE: AND THE OTHER THING IS THAT ISSUE OF SECRECY. AND I THINK IT'S VERY IMPORTANT TO DISTINGUISH SECRECY FROM CONFIDENTIALITY. CONFIDENTIALITY HAS ITS BASIS IN THE NEEDS OF SCIENTISTS AND IN INDUSTRY TO PROTECT ITS INTELLECTUAL PROPERTY AS WE HAVE TALKED ABOUT. AND WE ARE ADDRESSING THAT IN SOME WAYS BY REALLY TRYING TO FORCE THE DISEASE TEAMS TO BE MULTIDISCIPLINARY AND TO FORCE A DIALOGUE BETWEEN THOSE WHO ARE OPTIMIZING A PRODUCT FOR COMMERCIALIZATION AND THOSE WHO ARE COMMERCIALIZING IT. I THINK THAT -- AND

BEYOND THAT, AGAIN, THERE MAY BE SOME BETTER WAYS TO ENCOURAGE THE FLOW OF INFORMATION.

THOSE ARE THE THINGS WE'RE DOING SO THAT YOU CAN UNDERSTAND THAT IT'S NOT BECAUSE OF LACK OF EFFORT, BUT WE NEED HELP ON WHAT THE NEXT STEPS ARE.

CHAIRMAN LO: JEFF, LET ME GIVE YOU THE LAST COMMENT, AND THEN I WANT TO SORT OF MOVE ON BECAUSE WE HAVE OTHER SPEAKERS THAT WILL PICK UP ON SOME OF THESE THEMES.

MR. SHEEHY: I REALLY THINK, AT LEAST IN TERMS OF PUBLISHING OR MAKING AVAILABLE NEGATIVE RESULTS, WE'RE PROBABLY GOING TO HAVE TO RELY ON SOME SORT OF COMPULSION AS A CONDITION OF FUNDING. BECAUSE ONE OF THE FIRST THINGS I DID WHEN I CAME INTO MY JOB WAS HANDLE A SITUATION WHERE NEGATIVE RESULTS WERE UNPUBLISHABLE BECAUSE A COMPANY REFUSED TO ALLOW THE PI TO GET ACCESS TO ALL THE DIFFERENT TRIAL SITES. SO EVEN THE STRONG WILLINGNESS OF A PI TO REVEAL THE RESULTS, AND, IN FACT, THAT PRODUCT CONTINUED TO BE TESTED IN ANOTHER SETTING EVEN AFTER THEY HAD THE NEGATIVE RESULTS HERE AND REFUSED TO SHARE AND PUBLISH, THEY CONTINUED ON WITH THE CLINICAL TRIAL OF THAT PRODUCT IN A DIFFERENT SETTING.

SO I DO THINK -- AND THAT WAS SEVERAL

YEARS AGO, AND HERE WE ARE STILL TALKING ABOUT IT. I THINK IT WOULD BE A GOOD STANDARD FOR US TO AS MUCH AS POSSIBLE INCLUDE IN OUR GRANT AWARD THE COMPULSION TO PUBLISH NEGATIVE RESULTS. I DON'T THINK POSITIVE RESULTS WHICH ARE REALLY WHERE PEOPLE ARE CONCERNED IN TERMS OF INTELLECTUAL PROPERTY AND CONFIDENTIALITY, ETC. WE NEED TO WORRY ABOUT. IF THEY HAVE A POSITIVE RESULT, I THINK THAT THAT WILL COME OUT EVENTUALLY BECAUSE THAT'S OBVIOUSLY SOMETHING THEY'RE GOING TO CONTINUE DOWN THE ROAD WITH.

BUT THE NEGATIVE RESULTS, I THINK, WHERE WE ARE RUNNING THE RISK OF PEOPLE HAVING TO PARTICIPATE IN AN EXPERIMENT THAT WE ALREADY KNOW DOES NOT WORK IS SOMETHING THAT WE SHOULD BE REALLY FORCEFUL ON, I THINK.

CHAIRMAN LO: AGAIN, AS A POINT OF INFORMATION ON WHAT JEFF RAISED, THIS WAS A CLINICAL TRIAL AT UCSF. AND AS A RESULT OF THAT TRIAL AND TWO OTHER CLINICAL TRIALS, THE UNIVERSITY SET A POLICY THAT A CONDITION OF SIGNING A RESEARCH CONTRACT OR GRANT INCLUDED THE RIGHT OF THE INVESTIGATOR TO PUBLISH SUBJECT TO NOTIFYING THE SPONSOR AND ALSO GIVING THE SPONSOR, I THINK IT'S, A TWO-MONTH DELAY IF THEY REQUEST IT TO FILE A PATENT.

SO THERE'S AN ATTEMPT MADE TO BALANCE THE INTELLECTUAL PROPERTY RIGHTS OF THE INTERESTS OF THE COMPANY VERSUS THE INVESTIGATOR AND ULTIMATELY THE PUBLIC'S INTEREST IN KNOWING THE RESULT OF THE TRIAL. I'LL GIVE YOU THE LAST WORD.

DR. CHARO: LOOK WHAT YOU STARTED.

DR. KALICHMAN: I JUST WANT TO COME BACK TO ALMOST EVERYTHING WE'VE DISCUSSED HAS FOCUSED ON THE IDEA THAT WE NEED TO FIND WAYS TO GAIN CONSENSUS IS AN IMPORTANT ISSUE. AND THE IDEA OF A CONSENSUS CONFERENCE, THE CONFERENCE GRANTS IS POTENTIALLY A GREAT MECHANISM, BUT I KNOW FIRSTHAND THAT THERE ARE REPRESENTATIVES OF THREE INSTITUTIONS HERE TODAY WHO ARE PLANNING TO APPLY FOR ONE OF THESE CONFERENCE GRANTS WITH THE IDEA OF TRYING TO GET CONSENSUS ON SOME OF THE KEY ISSUES FACED BY AT LEAST THE ESCRO AN SCRO COMMITTEES IN THEIR REVIEW PROCESSES.

THAT IDEA HAS KIND OF SLOWED DOWN BECAUSE IT'S OCCURRING TO ME TODAY, AS I'M LISTENING TO THE DISCUSSION, THAT THE REASON IS THAT THIS IS REALLY SOMETHING THAT THOSE CONFERENCES SHOULD BE CONVENED BY CIRM, NOT DRIVEN BY, I WOULD ARGUE, FROM WHAT I'M HEARING TODAY, NOT DRIVEN BY AN INDIVIDUAL INSTITUTION SAYING WE'RE GOING TO PUT IN THE MONEY TO BE ABLE TO MATCH WHAT CIRM WILL PROVIDE, BUT

INSTEAD CIRM SHOULD SAY WE'RE GOING TO CONVENE THOSE DISCUSSIONS.

SO I WOULD ARGUE STRONGLY THAT ALL OF THE CONFERENCE GRANTS MAY HAVE CERTAIN PURPOSES. THIS MAY NOT BE ONE OF THEM, BUT THAT'S SOMETHING WE CAN DISCUSS MORE.

CHAIRMAN LO: OKAY. THANKS VERY MUCH. I WANT TO SORT OF MOVE US ALONG. I PROMISED A CHECK-OUT BREAK AT ELEVEN. SO STEVE PECKMAN IS THE GOING TO BE THE NEXT SPEAKER. AND, STEVE, WHAT WE MIGHT DO IS DO TWO-THIRDS OF YOUR TALK AND THEN HAVE A BREAK.

SO STEVE IS THE ASSOCIATE DIRECTOR OF THE UCLA SO-AND-SO STEM CELL RESEARCH INSTITUTE. I DON'T KNOW WHO YOUR DONOR IS.

DR. PECKMAN: ELI AND EDYTHE BROAD, THE CENTER OF REGENERATIVE MEDICINE AND STEM CELL RESEARCH.

CHAIRMAN LO: OH, GREAT.

DR. PECKMAN: OTHERWISE KNOWN AS SO-AND-SO.

CHAIRMAN LO: I DIDN'T WANT TO PRETEND THERE WASN'T SOMEONE. I DIDN'T WANT TO GIVE CREDIT TO THE WRONG PERSON. BUT THE BROAD FAMILY HAS BEEN VERY GENEROUS IN SUPPORTING STEM CELL RESEARCH IN

CALIFORNIA.

DR. PECKMAN: I'D LIKE TO FOLLOW UP ON THE UNIVERSITY POLICY REGARDING CONTRACT NEGOTIATION. ACTUALLY APPLIES TO THE ENTIRE UNIVERSITY OF CALIFORNIA. THERE ISN'T A CAMPUS WITHIN THE SYSTEM THAT IS ALLOWED TO NEGOTIATE A CONTRACT THAT LIMITS ACADEMIC FREEDOM AND THE PUBLICATION AND DISSEMINATION OF DATA. I DON'T KNOW IF THAT HOLDS FOR THE PRIVATE UNIVERSITIES, BUT IT CERTAINLY IS FOR THE UNIVERSITY OF CALIFORNIA.

CHAIRMAN LO: SO STEVE HAS BEEN MANAGING THE SCRO, AND BEFORE THAT HE SPENT A NUMBER OF YEARS WITH THE IRB AT UCLA AS THE ADMINISTRATOR THERE, SO HE BRINGS A BACKGROUND FROM BOTH THE IRB WORLD AND THE SCRO WORLD AND A LOT OF EDUCATION OF PEOPLE ON RESEARCH ETHICS. STEVE HAS A NUMBER OF TOPICS, AND WHAT HE'S GOING TO DO IS TO PRESENT SOME INFORMATION, GIVE US TIME TO ANSWER QUESTIONS, COMMENT, AND THEN TAKE THE SECOND CHUNK AND THE THIRD CHUNK. STEVE.

DR. PECKMAN: THANK YOU, BERNIE. ACTUALLY I WAS IN CHARGE OF THE UCLA IRB PROGRAM FOR 365 YEARS IN DOG YEARS. SO I'M GOING TO TALK ABOUT THE INSTITUTIONAL IMPLEMENTATION OF A LOT OF THINGS THAT WE'VE BEEN TALKING ABOUT YESTERDAY AND TODAY. AND I

WANT TO THANK MICHAEL FOR HIS EXCELLENT PRESENTATION BECAUSE IT LEADS INTO A LOT OF WHAT I'M GOING TO DISCUSS.

SO TO OUTLINE WHAT I'M GOING TO TALK ABOUT IS, FIRST, DO WE NEED TO REINVENT THE WHEEL? THERE'S AN INCREDIBLE WELL-ESTABLISHED, EFFECTIVE, ROBUST CLINICAL RESEARCH REVIEW SYSTEM IN PLACE THAT ACTUALLY MAY EVEN PREDATE SOME OF THE BIRTHS OF PEOPLE IN THIS ROOM. SO I THINK WE NEED TO THINK ABOUT THIS IN TERMS OF WHAT IS IN EXISTENCE AND MAYBE WHAT WE NEED TO STRONGLY SUGGEST PEOPLE DO THAT THEY MAY NOT BE DOING THAT THEY SHOULD BE DOING AND WAYS TO AUGMENT THAT. THE SYSTEM EXISTS THROUGH REGULATIONS FROM THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, OFFICE FOR HUMAN RESEARCH PROTECTIONS, THE FDA, WHICH WE'VE HEARD QUITE A LOT ABOUT OVER THE LAST TWO DAYS, AND CALIFORNIA ACTUALLY HAS THE CALIFORNIA MEDICAL EXPERIMENTATION ACT THAT HAS EXPLICIT STATE LAWS REGARDING DOING CLINICAL RESEARCH. AND THEN ALSO ACADEMIC MEDICAL CENTERS THAT SPECIFICALLY HAVE COMPREHENSIVE CANCER CENTERS ALSO REQUIRE SCIENTIFIC REVIEW AND MONITORING COMMITTEES OF HUMAN SUBJECTS RESEARCH.

SO I'M GOING TO FOCUS A LOT ON MY PREVIOUS JOB, WHICH IS WHAT THE INSTITUTIONAL REVIEW BOARD OR

THE IRB REVIEW IS ABOUT, AND HOW IT ADDRESSES A LOT OF THE QUESTIONS WE'VE BEEN TALKING ABOUT. AND I'LL TOUCH UPON WHAT IS AN IRB MADE UP OF, WHO ARE THOSE PEOPLE, WHAT ARE THEIR EXPERTISE, HOW THEY PERFORM A RISK-BENEFIT CALCULATION, HOW THEY DETERMINE SUBJECT SELECTION, INFORMED CONSENT, A DISCUSSION OF INVESTIGATOR CONFLICT OF INTEREST, WHAT WE DO ABOUT INJURED RESEARCH SUBJECTS, WHICH MAY BE AN IMPORTANT ELEMENT OF STEM CELL RESEARCH, AND HOW WE ACCOMPLISH CONTINUING REVIEW OR THE ONGOING MONITORING OF THIS RESEARCH. AND THEN, FINALLY, I'D LIKE TO HIT UPON NAVIGATING OLD AND NEW COMPLIANCE COMMITTEES, AND WHERE ACTUALLY DOES A SCRO FIT IN IN THIS CALCULATION IN THAT SCRO'S WERE DEVELOPED ORIGINALLY BY THE NAS, LATER ADOPTED BY CIRM, BUT SPECIFICALLY FOCUSED ON LABORATORY RESEARCH AND PRECLINICAL RESEARCH. AND ACTUALLY THE COMPOSITION AND THE CONCEPTUALIZATION OF SCRO'S REALLY DO TAKE INTO ACCOUNT CLINICAL RESEARCH.

SO THE INSTITUTIONAL COMPLIANCE COMMITTEES THAT ARE GOING TO BE INVOLVED IN THIS CLINICAL RESEARCH INCLUDE THE IRB, THE IACUC, WHICH WE TALKED ABOUT YESTERDAY, THE INSTITUTIONAL BIOSAFETY COMMITTEE, THE MEDICAL RADIATION SAFETY COMMITTEE. MANY OF THE TRIALS THAT ARE GOING TO HAPPEN WITH

CELLS ARE GOING TO REQUIRE SOME KIND OF TRACKING THROUGH RADIOACTIVE PROCESSES LIKE PET SCANS, WHICH WOULD THEN REQUIRE A RADIATION COMMITTEE TO REVIEW THE PROJECT AS WELL.

AS I INDICATED PREVIOUSLY, THE SCIENTIFIC PEER REVIEW COMMITTEE, MANY CAMPUSES HAVE GENE MEDICINE COMMITTEES FOR THOSE PROJECTS THAT WILL REQUIRE GENETIC MANIPULATION OF CELLS, AND THEN THERE'S ALSO CONFLICT OF INTEREST COMMITTEES, BUT I'M GOING TO SPECIFICALLY TALK ABOUT A CONFLICT OF INTEREST THAT THOSE COMMITTEES DON'T ADDRESS. AND THEN FINALLY, OUR EVER FAITHFUL AND NEW STEM CELL RESEARCH OVERSIGHT COMMITTEES.

SO IRB'S OPERATE UNDER THREE ETHICAL PRINCIPLES THAT WERE PROMULGATED IN THE 1970S AS A RESULT OF THE NATIONAL RESEARCH ACT THAT WAS PUT FORTH BY PRESIDENT RICHARD NIXON. AND THOSE ETHICAL PRINCIPLES INCLUDE BENEFICENCE, JUSTICE, AND RESPECT FOR PERSONS. AND THIS IS THE ORDER IN WHICH I'M GOING TO COVER THEM.

BENEFICENCE IS WEIGHING THE RISKS AND BENEFITS OF RESEARCH. JUSTICE IS THE EQUAL DISTRIBUTION OF THOSE RISKS AND BENEFITS ACROSS PATIENT POPULATIONS OR OUR POPULATION IN GENERAL. AND FINALLY, RESPECT FOR PERSONS, WHICH IS A CONCEPT

OF THE DIGNITY AND AUTONOMY OF INDIVIDUAL PEOPLE.

FIRST, IRB REVIEW. WHO IS THE IRB? WELL, BY REGULATION THE IRB IS REQUIRED TO BE SUFFICIENTLY QUALIFIED THROUGH THEIR EXPERIENCE AND EXPERTISE AND DIVERSITY TO SAFEGUARD THE RIGHTS AND WELFARE OF SUBJECTS, WHICH IMPLICITLY MEANS THAT THEY HAVE TO HAVE SUFFICIENT SCIENTIFIC EXPERTISE AND KNOWLEDGE OF THE PATIENT POPULATION IN ORDER TO REVIEW THE RESEARCH. THEY HAVE TO HAVE PROFESSIONAL COMPETENCE TO REVIEW AND ASSESS THE RESEARCH IN TERMS OF INSTITUTIONAL COMMITMENTS, SUCH AS THOSE CONTRACT REQUIREMENTS THAT DATA BE MADE AVAILABLE, REGULATIONS AND APPLICABLE LAW THAT I TOUCHED UPON EARLIER, AND STANDARDS OF PROFESSIONAL CONDUCT AND PRACTICE.

THEY'RE REQUIRED TO ENSURE THE EFFECTIVE SELECTION OF SUBJECTS. THEY HAVE TO ASSESS THE APPROPRIATE SELECTION. AS WE TALKED ABOUT YESTERDAY, DO WE INCLUDE PATIENTS IN CLINICAL TRIALS IN PHASE I OR NONPATIENTS, HEALTHY VOLUNTEERS? IF WE'RE INCLUDING PATIENTS, THERE'S A PATIENT-PATIENT CALCULUS THAT HAS TO BE PERFORMED. DO WE INCLUDE OLDER PATIENTS OR YOUNGER PATIENTS? ADULTS OR MINORS? EARLIER OR LATER DISEASE? PEOPLE WHO HAVE RECEIVED STANDARD OF CARE OR PEOPLE WHO ARE

TREATMENT NAIVE? ALL OF THESE THINGS NEED TO BE ASSESSED BY THE IRB.

THEY'RE GOING TO PERFORM A RISK-BENEFIT CALCULATION. THE IDEA OF THIS RISK-BENEFIT CALCULATION, OF COURSE, PROBABLY COULD GO ALL THE WAY BACK TO HIPPOCRATES AND THE IDEA OF DO NO HARM. BUT IF WE ACTUALLY APPLIED DO NO HARM TO CLINICAL RESEARCH, WE WOULDN'T BE DOING ANY CLINICAL RESEARCH.

SO AFTER WORLD WAR II THERE WAS THE DEVELOPMENT OF THE NUREMBERG CODE WHICH HAD EXPLICIT CONCEPTS FOR RISK-BENEFIT CALCULATION. FOLLOWING THAT IN THE 1970S THE BELMONT REPORT WITH ADDITIONAL ELEMENTS OF RISK-BENEFIT CALCULATION, INCLUDING THE CONCEPT THAT RISK MAY INCLUDE HARM, PSYCHOLOGICAL, PHYSICAL, SOCIAL, LEGAL, OR ECONOMIC. THE IRB IS RESPONSIBLE FOR ASSESSING THOSE RISKS AND MINIMIZING THOSE RISKS WHERE POSSIBLE WHILE MAXIMIZING BENEFITS.

THEY ALSO HAVE TO ENSURE AND INSIST UPON JUSTIFICATION OF THE RISK AND POSSIBLE BENEFITS TO THE SUBJECTS THROUGH THE PERFORMANCE OF RESEARCH THAT IS VALID, THAT THEY'RE GOING TO COME UP WITH A VALID RESEARCH QUESTION THAT WILL RESULT IN SOME KNOWLEDGE THAT WILL BENEFIT HUMANITY.

THE DECLARATION OF HELSINKI FOLLOWED, AND IT NOTED EXPLICITLY THAT WE SHOULD CEASE RESEARCH IF RISKS ARE FOUND TO OUTWEIGH POTENTIAL BENEFITS OR CONCLUSIVE APPROVE OF A POSITIVE OR NEGATIVE RESULT. AND THIS IS WHERE ONGOING MONITORING OF THE RESEARCH IS CRUCIAL.

SO WHAT ARE THE FEDERAL REGULATIONS? RESEARCH MAY BE JUSTIFIED IF THE RISKS ARE REASONABLE IN RELATION TO ANTICIPATED BENEFITS TO SUBJECTS AND THE IMPORTANCE OF THE KNOWLEDGE REASONABLY EXPECTED TO RESULT. THE EVALUATION, ONLY THOSE RISKS AND BENEFITS THAT RESULT FROM THE RESEARCH SHOULD BE EVALUATED. AND THEY SHOULD NOT INCLUDE STANDARD THERAPIES THAT SUBJECTS WOULD OTHERWISE RECEIVE.

AND WHAT ARE THE TOOLS OF REVIEW? AMIDST ALL THE SECRECY THAT WE'VE BEEN TALKING ABOUT, ACTUALLY THE IRB LIFTS THAT CLOAK OF SECRECY. BECAUSE IN ORDER TO DO A CLINICAL TRIAL WITH A DRUG DEVICE OR BIOLOGIC, THE MANUFACTURER WHO WANTS TO PERFORM THE TRIAL OR THE INVESTIGATOR MUST PROVIDE AN INVESTIGATOR'S BROCHURE WHICH ACTUALLY INCLUDES ALL THAT TOP SECRET SECRET SAUCE INFORMATION. THE IRB KNOWS WHAT'S IN THE SECRET SAUCE AND THEY KNOW HOW YOU MADE THE SECRET SAUCE AND HOW YOU GOT THERE.

SO THERE HAS TO BE SUFFICIENT PRECLINICAL STUDIES IN RELEVANT ANIMAL MODELS, AND THERE SHOULD BE MANUFACTURER AND POTENCY OF CELL PRODUCT INFORMATION IN ORDER FOR THE IRB TO ACTUALLY ASSESS THIS INFORMATION, AND THERE SHOULD BE CONTINUING REVIEW, WHICH I'LL TALK A LOT MORE ABOUT LATER.

AND THEN THERE ARE FEDERAL GUIDELINES REGARDING DATA AND SAFETY MONITORING PLANS, WHICH I WILL ALSO TALK ABOUT LATER. ALL OF THOSE GO INTO ACTUALLY ASSESSING THE RISKS AND BENEFITS OF RESEARCH AND PROTECTING HUMAN SUBJECTS.

SO ONE OF THE PRIMARY ROLES, OF COURSE, THAT WE'RE GOING TO HAVE TO ADDRESS IS MANAGING THE EXPECTATIONS OF OUR PUBLIC, THOSE WONDERFUL PEOPLE WHO VOTED FOR PROP 71 AND THOSE WHO DIDN'T, EVERYONE WHO MAY BE IMPACTED BY THIS RESEARCH.

NOW, OF COURSE, *TIME MAGAZINE* IN 2006 WROTE ABOUT THE HYPE AND THE HYPE ALONG WITH MANY OTHER MAGAZINES AND WHAT IT MEANS FOR THE PUBLIC. WE'VE COME A LONG WAY IN THREE YEARS. NOW *TIME MAGAZINE* IS TALKING ABOUT STEM CELLS SAVING OUR LIVES. SO IRB'S ARE ALSO RESPONSIBLE FOR MANAGING THESE EXPECTATIONS, AND THEY'RE GOING TO MANAGE THESE EXPECTATIONS THROUGH THE SELECTION, APPROPRIATE SELECTION, OF SUBJECTS AND ACCURATE,

INFORMATIVE, AND UNDERSTANDABLE INFORMED CONSENT.

SO INFORMED CONSENT, IT'S RESPECT FOR A PERSON'S DIGNITY AND AUTONOMY. THE NUREMBERG CODE SAYS THAT THE VOLUNTARY CONSENT OF THE HUMAN SUBJECT IS ABSOLUTELY ESSENTIAL. IN FACT, IN OUR CURRENT AGE IT'S ASSUMED THAT PEOPLE WILL GIVE INFORMED CONSENT FOR PARTICIPATION IN CLINICAL RESEARCH. THE BELMONT REPORT TOLD US THAT WE NEED TO TREAT INDIVIDUALS AS AUTONOMOUS AGENTS, AND PERSONS WITH DIMINISHED AUTONOMY ARE ENTITLED TO EXTRA PROTECTION.

AUTONOMY IS AN INTERESTING QUESTION THOUGH, ESPECIALLY IN THE STATE OF CALIFORNIA. AND I'LL TALK ABOUT THE DIVERSITY OF THE STATE AND HOW IRB'S HAVE TO ADDRESS THAT DIVERSITY.

THE FEDERAL REGULATIONS STATE THAT NO INVESTIGATOR MAY INVOLVE A HUMAN BEING AS A SUBJECT IN RESEARCH COVERED BY THESE REGULATIONS UNLESS THE INVESTIGATOR HAS OBTAINED THE LEGALLY EFFECTIVE INFORMED CONSENT OF THE SUBJECT OR THE SUBJECT'S LEGALLY AUTHORIZED REPRESENTATIVE. AND THE INFORMATION THAT'S GIVEN TO THE SUBJECT OR THE REPRESENTATIVE SHALL BE IN A LANGUAGE UNDERSTANDABLE TO THE SUBJECT. SO I'M GOING TO TOUCH UPON NOW WHAT IS LEGALLY EFFECTIVE INFORMED CONSENT AND WHAT DOES

IT MEAN TO BE IN A LANGUAGE THAT'S UNDERSTANDABLE TO THE SUBJECT. THESE ARE ALL IMPORTANT ISSUES THAT HAVE TO BE PART OF THE CALCULATION OF THE CONDUCT OF RESEARCH.

SO THESE ARE THE LEGALLY EFFECTIVE ELEMENTS OF INFORMED CONSENT. I'M SURE YOU'RE VERY FAMILIAR WITH THEM. THEY'RE ALL VERY REASONABLE THINGS THAT ANY REASONABLE PERSON WOULD WANT TO BE TOLD BEFORE THEY SUBJECT THEMSELVES TO AN EXPERIMENT. AND THESE ARE ALL IN THE FEDERAL REGULATIONS AND APPROPRIATE BY THE CALIFORNIA MEDICAL EXPERIMENTATION ACT. THEY'RE ALSO REFERRED TO WITHIN CIRM'S REGULATIONS AS WELL.

SO WHEN WE TALK ABOUT INFORMED CONSENT OR ASSENT FOR MINORS OR OTHERS WHO AREN'T CAPABLE OF GIVING INFORMED CONSENT, WE'RE TALKING ABOUT MORE THAN A DOCUMENT. WE'RE TALKING ABOUT MORE THAN A CONTRACT OR A PIECE OF PAPER. WHAT WE'RE TALKING ABOUT IS A PROCESS OF COMMUNICATION. WE'RE TALKING ABOUT A PROCESS OF COMMUNICATION THAT BEGINS WITH THE IDENTIFICATION OF POTENTIAL SUBJECTS, HOW WE ADVERTISE FOR THEM, HOW WE RECRUIT THEM, AND HOW WE CREATE AN ENVIRONMENT FOR A DIALOGUE ABOUT WHAT IT MEANS TO PARTICIPATE IN RESEARCH IN GENERAL AND A SPECIFIC PROJECT.

HAS TO ENSURE COMPREHENSION THAT EMPOWERS THE SUBJECT'S KNOWLEDGEABLE DECISION-MAKING. WHAT IS THAT KNOWLEDGEABLE DECISION-MAKING? YOU DO NOT HAVE AUTONOMY, AND YOUR DIGNITY IS TAKEN AWAY. AND FUNDAMENTALLY IT HAS TO ENSURE VOLUNTARINESS.

SO WHAT IS THE CONTEXT OF CONSENT? AS MCPHERSON AND CONNOLLY NOTED, LANGUAGE AND CULTURE HAVE SUBTLE IMPLICATIONS FOR DISCLOSURE AND CONSENT. AS THE BELMONT REPORT REMINDED US, BECAUSE THE SUBJECT'S ABILITY TO UNDERSTAND IS A FUNCTION OF INTELLIGENCE, RATIONALITY, MATURITY, AND LANGUAGE, IT IS NECESSARY TO ADAPT THE PRESENTATION OF THE INFORMATION TO THE SUBJECT'S CAPACITIES, WHICH REQUIRES IRB'S, INVESTIGATORS, SPONSORS, AND INSTITUTIONS TO BE CREATIVE IN ORDER TO HAVE FUNDAMENTAL AND GOOD COMMUNICATION.

SO WHAT DOES THE POPULAR PRESS TELL US ABOUT THE POTENTIAL SUBJECT POPULATION IN THE STATE OF CALIFORNIA? 224 LANGUAGES SPOKEN IN THE STATE. 40 PERCENT OF L.A. COUNTY RESIDENTS ARE BORN IN ANOTHER COUNTRY. AND THOSE ARE THE FRONT LINES OF PATIENT CARE DON'T MAP OUT THE COMMUNICATION GAP EXISTS. SO IT'S UP TO THE IRB INVESTIGATORS TO CLOSE THAT COMMUNICATION GAP.

WHO ARE THE SUBJECTS? THERE ARE BASIC

DEMOGRAPHIC ASSUMPTIONS WE ALL MAKE. IN THE 1940S IN CALIFORNIA, 90 PERCENT OF CALIFORNIA POPULATION WAS EURO-AMERICAN. IN THE 1990S WE'VE SEEN UNPRECEDENTED DEMOGRAPHIC CHANGES, AND NOW THE POPULATION HAS CHANGED, AND EURO-AMERICANS ARE THE MINORITY.

AND THIS CHANGING TREND CHALLENGES US TO QUESTION ASSUMPTIONS OF MINORITY VERSUS MAJORITY AS WELL AS HOMOGENEOUS EURO-AMERICAN VALUE SYSTEMS THAT MAY NOT BE APPLICABLE TO COMMUNITIES OF COLOR. THIS ALL GOES INTO THE CALCULUS OF HOW WE RESPECT THE DIGNITY AND AUTONOMY OF INDIVIDUALS WHO ARE GOING TO BE IN OUR RESEARCH.

FURTHERMORE, ONE IN TEN ADULTS IN L.A. HAVE SIX YEARS OF EDUCATION OR LESS. IT'S THE WORST OF ALL MAJOR CITIES IN THE U.S. 53 PERCENT OF ALL WORKING AGE L.A. COUNTY RESIDENTS HAVE TROUBLE READING STREET SIGNS OR BUS SCHEDULES, FILLING OUT JOB APPLICATIONS, OR UNDERSTANDING A UTILITY BILL. I HAVE TO SAY, I DO ALL RIGHT WITH THE BUS SCHEDULE AND I DO HAVE A JOB, BUT MY UTILITY BILL IS STILL MYSTIFYING TO ME. AND SO WE HAVE TO THINK ABOUT THE LEVELS OF INFORMATION WE ARE GOING TO GIVE PEOPLE AND HOW THEY'RE GOING TO UNDERSTAND IT TO MAXIMIZE THEIR AUTONOMY AND DIGNITY. AND THIS IS WHAT THE

IRB'S DO EVERY DAY.

SO WHAT DO WE UNDERSTAND? WELL, THE FOLKS IN THIS ROOM COULD PROBABLY RELATE TO THESE STATISTICS. PERCENTAGE OF ADULTS WITH GRADUATE SCHOOL EXPERIENCE WHO ARE RATED PROFICIENT IN PROCESS READING DROPPED BY TEN POINTS ACCORDING TO 2007 STATISTICS. NUMBER OF ADULTS WITH A COLLEGE DEGREE AND PROFICIENT READING OF PROCESS DROPPED FROM 40 PERCENT TO 31 PERCENT IN 2003, AND ON AVERAGE AMERICANS AGE 15 TO 24 SPEND ALMOST TWO HOURS A DAY WATCHING T.V. AND ONLY SEVEN MINUTES OF THEIR LEISURE TIME READING.

SO CLEARLY IT REQUIRES IRB'S TO THINK ABOUT NOVEL PROPOSALS TO DISSEMINATING INFORMATION, INCLUDING VIDEO AND AUDIO, THE USE OF PICTURES, DIAGRAMS, AND CHARTS. PEOPLE ARE BECOMING LESS ACCUSTOMED TO READING. SO HOW DO WE OBTAIN INFORMED CONSENT AND ENSURE THERE'S INFORMED CONSENT?

IN THIS CONTEXT WE HAVE A CHANGING VISION OF RESEARCH. IN THE 1970S THE BELMONT REPORT STRONGLY ENCOURAGED US NOT TO SEE RESEARCH AS TREATMENT, TO SEE RESEARCH AS A BURDEN TO POPULATIONS, THAT WE SHOULD BE PROTECTIONIST OF SUBJECTS, AND WE SHOULD BE HIGHLY EXCLUSIONARY. AND WE HAVE TO REMEMBER THE CONTEXT IN WHICH THE BELMONT

REPORT WAS WRITTEN. THERE WAS INCREDIBLE REPORTS OF UNETHICAL RESEARCH IN THE U.S., INCLUDING THE MOST FAMILIAR PROJECT BY THE PUBLIC HEALTH SERVICE, WHICH WAS THE NATURAL HISTORY OF THE SYPHILIS TRIAL.

SO THE CONTEXT OF THE BELMONT REPORT WAS INTERESTING AND IMPORTANT. BUT IN THE 1980S WE HAD A CHANGE IN THE RESEARCH ENVIRONMENT WITH THE AIDS CRISIS WHERE, BECAUSE THERE WAS NO EFFECTIVE TREATMENT, NO EVEN CONCEPT OF HOW TO TREAT THE DISEASE, AND PEOPLE WERE DYING IN INCREDIBLY LARGE NUMBERS VERY QUICKLY, RESEARCH BECAME THE ONLY MODE OF TREATMENT.

RESEARCH BECAME A BENEFIT. IT WAS A RIGHT TO BE INCLUDED. BUT I THINK WE HAVE TO REMIND OURSELVES THAT IT'S NECESSARY TO STRIKE A BALANCE BETWEEN THESE TWO EPISODES IN HISTORY AS NOT EVERY DISEASE IS GOING TO RESULT IN IMMEDIATE MORTALITY OR IRREVERSIBLE MORBIDITY. AND THAT MAYBE SOME SUBJECT POPULATIONS, AS HAS BEEN DISCUSSED OVER THE LAST TWO DAYS, AND WE WERE REMINDED OF IN MICHAEL'S PRESENTATION, MAYBE SHOULDN'T BE THE FIRST TO RECEIVE STEM CELLS.

WHAT WE'RE TALKING ABOUT HERE WITH RESEARCH AND TREATMENT IS THE THERAPEUTIC MISCONCEPTION WHICH WAS FIRST COINED BY PAUL

APPLEBAUM A COUPLE DECADES AGO. EFFECTIVELY THE OHRP IRB GUIDEBOOK REMINDS US THAT RESEARCH ITSELF IS NOT THERAPEUTIC. FOR ILL PATIENTS, RESEARCH INTERVENTIONS MAY OR MAY NOT BE BENEFICIAL. INDEED, THE PURPOSE OF EVALUATIVE RESEARCH IS TO DETERMINE WHETHER THE TEST INTERVENTION IS, IN FACT, THERAPEUTIC. AND FRANK MILLER TOLD US IN *JAMA* IN 1998, NOW 11 YEARS AGO -- MY, HOW TIME FLIES -- IT IS ETHICALLY PROBLEMATIC IF BOTH INVESTIGATORS AND PATIENT VOLUNTEERS SEE RESEARCH FROM AN EXCLUSIVELY THERAPEUTIC PERSPECTIVE. IN THE FACE OF THIS POTENTIAL DIVERGENCE BETWEEN PURSUING PATIENT-CENTERED BENEFICENCE AND SCIENTIFIC KNOWLEDGE, THE ORIENTATION OF INVESTIGATORS AS CLINICIANS CAN PROMOTE A FORM OF COGNITIVE DISSONANCE. AND WHAT WE WANT TO AVOID IS THAT COGNITIVE DISSONANCE. AND WHAT IRB'S ARE CHALLENGED WITH IS THE IMPORTANCE OF ENSURING AGAIN THAT PEOPLE UNDERSTAND WHAT IT IS THEY'RE ABOUT TO EMBARK ON.

AND SO HOW DO THEY DO THAT? FOR PHASE I RESEARCH, WE TALKED ABOUT THAT A LOT YESTERDAY, IT'S THE FIRST USE TYPICALLY OF A POTENTIAL TEST ARTICLE IN HUMAN BEINGS. WHAT IS THE PURPOSE OF A PHASE I CLINICAL TRIAL? TREATMENT? IS IT TO STUDY? IS IT TO PERFORM RESEARCH? IS IT AN EXPERIMENT? WOULD

YOU BE AMAZED IF I TOLD YOU THAT THERE'S LOTS OF DATA OUT THERE THAT TELL YOU THAT PEOPLE RESPOND TO THOSE FOUR WORDS DIFFERENTLY? AND THAT ALL FOUR OF THOSE WORDS HAVE BEEN USED IN PHASE I INFORMED CONSENT FORMS REVIEWED BY IRB'S. AND I THINK WE NEED TO ASK OURSELVES WHAT WORD IS PREFERABLE FOR A PHASE I CLINICAL TRIAL.

ARE WE GOING TO ENGAGE IN TREATMENT OR ARE WE GOING TO ENGAGE IN AN EXPERIMENT? WHAT IS PHASE I? PHASE I, AS WE WERE TOLD YESTERDAY, IS TESTING FOR SAFETY. WHAT IS IT TO TEST FOR SAFETY? WE'RE GOING TO FIND THE MAXIMUM TOLERATED DOSE OFTEN. THAT'S WHAT TYPICALLY HAPPENS IN CANCER TRIALS AND HIV TRIALS. BUT WHAT DOES IT MEAN TO FIND THE MAXIMUM TOLERATED DOSE? IT MEANS TYPICALLY YOU ARE GOING TO DOSE INDIVIDUALS OR GROUPS UNTIL YOU MAKE THEM SICK, TYPICALLY VERY SICK, AND THEN HOPEFULLY STOP AND DRAW BACK BEFORE YOU MAKE THEM IRREVERSIBLY SICK OR YOU KILL THEM. AND I CAN TELL YOU THAT PEOPLE DO DIE IN PHASE I RESEARCH.
THIS IS THE ULTIMATE ALTRUISTIC ACT.

IT'S IMPORTANT TO BE ABLE TO CONVEY INFORMATION TO SUBJECTS SO THEY UNDERSTAND WHAT IT MEANS TO BE THE FIRST PERSON TO RECEIVE A TEST ARTICLE. WHAT WE FOUND IN PHASE I ONCOLOGY TRIALS

IN RESEARCH -- BECAUSE THERE IS A LOT OF RESEARCH BEING DONE ON IRB'S, IT SEEMS TO BE THE FAVORITE PURVIEW OF A WHOLE LOT OF FOLKS OVER THE LAST TEN YEARS AND SPECIFICALLY INFORMED CONSENT.

SO WHAT DOES THIS RESEARCH TELL US? IN PHASE I ONCOLOGY TRIALS, CONSENT FORMS ALMOST NEVER PROMISE DIRECT BENEFIT TO THE SUBJECTS. IT'S NICE TO HEAR. I FEEL REASSURED. THEY RARELY MENTION CURE AND USUALLY COMMUNICATE THE SERIOUSNESS AND UNPREDICTABILITY OF RISK. BUT THE AUTHORS WARREN AND COLLEAGUES IN THE *NEW ENGLAND JOURNAL* REMIND US THERE'S ROOM FOR IMPROVEMENT.

THE SUBSTANCE OF THESE FORMS IS UNLIKELY TO BE THE PRIMARY SOURCE OF MISUNDERSTANDING BY SUBJECTS IN PHASE I ONCOLOGY TRIALS. SO WHAT IS THAT PRIMARY SOURCE OF MISUNDERSTANDING? IT'S THE THERAPEUTIC MISCONCEPTION. AND IT'S BROUGHT NOT ONLY BY THE PATIENT SUBJECT TO THE TRIAL, BUT THE CLINICIAN INVESTIGATOR WHO FIRMLY BELIEVES THAT THIS PRODUCT IS GOING TO HELP THIS PATIENT. BOTH MUST BE AVOIDED.

GOING FURTHER TO PHASE I HUMAN GENE TRANSFER RESEARCH, WHAT KIND OF THINGS DO WE FIND OUT ABOUT THOSE INFORMED CONSENT PROCESSES? THERAPEUTIC MISCONCEPTION MAY BE QUITE BIG. THERE'S

GREATER UNCERTAINTY AND HAZARD IN THESE PROJECTS, AND THEY ENROLL PEOPLE WITH ADVANCED DISEASE SIMILAR TO CANCER WHO ARE MORE SUSCEPTIBLE TO THE MISCONCEPTION. BIOTECHNOLOGIES REGARDED BY CLINICIANS AND THE PUBLIC AS HERALDING REVOLUTIONARY ADVANCE SUCCUMB TO THE IDEA THAT NEW IS BETTER. AND THAT CLINICIANS WHO DEVELOP NOVEL APPROACHES OFTEN CONDUCT THEIR OWN CLINICAL TRIALS. THOSE PEOPLE WHO ARE ACTUALLY CREATING THE CELL-BASED PRODUCTS ARE GOING TO CONDUCT THE CLINICAL TRIAL. AND WE'RE GOING TO TALK ABOUT THAT CONFLICT OF INTEREST IN A MINUTE.

SO WHAT DOES APPLEBAUM HAVE TO SAY ABOUT HIS RESEARCH IN RANDOMIZED CLINICAL TRIALS? HE ACTUALLY GAVE US SOME EXCERPTS OF INTERVIEWS. INTERVIEWER CLARIFYING THE PREVIOUS RESPONSE OF THE PATIENT. SO THE CHOICE OF TREATMENT DOES DEPEND ON WHAT EACH INDIVIDUAL NEEDS AND THE SUBJECT RESPONDS I THINK SO, YES. I THINK THEY DO TAKE INTO ACCOUNT WHAT EACH PERSON NEEDS. IT'S A RANDOMIZED CLINICAL TRIAL.

SUBJECT NO. 112, I THINK IT'S A WIN-WIN FOR ANYBODY. I DON'T THINK THEY WOULD ASK YOU TO DO THIS OR PRESENT THIS TO YOU IF THEY DIDN'T THINK IT WAS GOING TO HELP YOU. INTERVIEWER: SO DO YOU

THINK THAT THEY ARE GIVING EVERYONE THE BEST TREATMENT? RESPONDENT: I DON'T THINK THEY'D BE IN THIS IF THEY DIDN'T. YOU KNOW, IT'S JUST LIKE BEING A DOCTOR WITH A SIGN ON THE DOOR. YOU KNOW THEY'RE HEALERS.

SO THIS IS THE ENVIRONMENT IN WHICH WE LIVE IN EVERY DAY. THIS IS THE ENVIRONMENT IN WHICH WE HAVE TO OPTIMIZE DIGNITY AND AUTONOMY AND MAKE SURE KNOWLEDGEABLE DECISION-MAKING IS OCCURRING BECAUSE THE FORCE AGAINST THESE CONCEPTS OF THERAPEUTIC MISCONCEPTION AND PHILOSOPHICAL CONSTRUCTS OF RESPECT FOR PERSONS BUTT UP AGAINST THE ETERNAL NEED FOR HOPE.

RESEARCH ACRONYMS. SPONSORS AND NOW INVESTIGATORS THEMSELVES ARE VERY INTERESTED IN SELLING THEIR RESEARCH BECAUSE IT'S IMPORTANT TO PROMOTE ENROLLMENT. WITHOUT PEOPLE WILLING TO PARTICIPATE IN RESEARCH, THE RESEARCH WILL NOT GET DONE. SO THIS IS WHERE CLINICAL RESEARCH MEETS MARKETING STRATEGIES AND ENGAGES A THERAPEUTIC MISCONCEPTION FOR THE BENEFIT OF ENROLLMENT.

SO MY FAVORITE ONE IS A STUDY CALLED CURE. WHO DOESN'T WANT TO BE IN CURE? CLOPIDOGREL AND UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS. I WANT TO BE IN SURVIVE, SURVIVAL OF PATIENTS WITH ACUTE

HEART FAILURE IN NEED OF INTRAVENOUS INOTROPIC SUPPORT. AND THEN THERE'S OPSOM, BRILLIANT, CASH, COURAGE, PROTECT, PROSPER, BIGGER, BIGMACK, HERO, CABBAGE PATCH, AND ALIVE.

WHEN I WAS WITH THE IRB, I HAVE TO SAY WE REVIEWED ALMOST ALL THOSE STUDIES EXCEPT FOR BIGMACK AND CABBAGE PATCH.

DR. WAGNER: OH, I THINK YOU DID. YOU JUST DIDN'T REALIZE IT.

DR. PECKMAN: I'M SORRY?

DR. WAGNER: I THINK YOU DID ACTUALLY THE CABBAGE PATCH.

DR. PECKMAN: AND I CAN TELL YOU IN EACH ONE WE TOLD THE INVESTIGATOR THEY COULD NOT USE THOSE TITLES IN THEIR INFORMED CONSENT FORM, AND MANY IRB'S ARE GOING UP AGAINST THIS IN TERMS OF CORPORATE SPONSORS, AND THEY'RE WINNING. BUT THEY HAVE TO ASK THE QUESTION IS MARKETING TAKING OVER APPROPRIATE DECISION-MAKING? THIS IS WHERE THE IRB RUBBER MEETS THE ROAD. AND THIS IS WHERE INVESTIGATORS ARE CONSTANTLY CLAIMING THAT THE IRB'S ARE OBSTRUCTIONIST ABOUT PETTY LITTLE ITEMS THAT ARE OF NO CONSEQUENCE. AFTER ALL, THIS IS WHAT THE SPONSOR CALLS THE PROJECT. IT'S ACCURATE.

THESE ARE SOME OF THE THINGS THAT WE HAVE

TO ENGAGE IN AS A GROUP OF THE STANDARDS WORKING GROUP, AS IRB'S, AS INVESTIGATORS, AS PATIENT ADVOCATES, AS THE PUBLIC TO ENSURE AUTONOMY AND DIGNITY.

EXPLAINING THE RISKS AND BENEFITS IN PHASE I RESEARCH. BENEFITS, THERE IS NO INTENT TO PROVE EFFECTIVENESS. THERE'S NO DIRECT BENEFIT INTENDED. SUBJECTS MAY EXPERIENCE A PSYCHOLOGICAL BENEFIT FROM THEIR ALTRUISTIC PARTICIPATION, PARTICIPATION ON BEHALF OF OTHERS. THIS IS WHAT PHASE I CLINICAL RESEARCH IS ABOUT.

RISKS, THE IRB HAS TO GATHER THESE RISKS, ASSESS THEM, AND THEN CONVEY -- MAKE SURE THEY'RE CONVEYED APPROPRIATELY TO SUBJECTS. AND WE COVERED SOME OF THESE YESTERDAY AND ALREADY THIS MORNING, THAT THERE MAY BE UNKNOWN TOXICITIES, THAT THERE MAY BE KNOWN TOXICITIES FROM SIMILAR RESEARCH OR RELEVANT ANIMAL MODELS, BUT WE'RE NOT SURE. THERE MAY BE AN INABILITY TO CONTROL PROLIFERATION OF CELLS AND WHAT THE OUTCOME OF THAT INABILITY MAY BE. AND YOU MAY HAVE A WORSENING CONDITION OR DISABILITY AS A RESULT OF PARTICIPATING IN THE RESEARCH.

THE ISSCR GUIDELINES, WHICH WE'LL HEAR ABOUT A LITTLE LATER, GO EVEN FURTHER IN TERMS OF THE NEED FOR IRB'S AND FOR INVESTIGATORS TO ASSESS

AND ACKNOWLEDGE THE NOVELTY AND UNPREDICTABILITY OF STEM CELL-BASED RESEARCH IN A SERIES OF VERY SPECIFIC TARGETS.

ALTERNATIVES TO RESEARCH. ONE OF THE MOST IMPORTANT ASPECTS OF INFORMED CONSENT, STANDARD OF CARE MAY BE AN AUTHENTIC ALTERNATIVE TO RESEARCH, ESPECIALLY FOR PATIENTS WHO ARE TREATMENT NAIVE OR HAVE NOT RECEIVED ALL OF THE STANDARDS OF POSSIBLE CARE. IF THERE'S A TERMINAL ILLNESS INVOLVED IN THE PATIENT POPULATION, AN ALTERNATIVE MAY BE PALLIATIVE CARE, TREATMENT OF SYMPTOMS AND PAIN CONTROL. WE NEED TO REMIND OURSELVES IN OUR QUEST TO HELP PATIENTS THAT PARTICIPATION IN RESEARCH MAY MAKE THEM WORSE. AND IT MAY DIMINISH WHATEVER QUALITY OF LIFE THEY HAVE REMAINING. BECAUSE THOSE LAST FEW MONTHS WITH ONE'S FAMILY AND FRIENDS AT FULL CAPACITY MAY BE MORE WELCOME BY THE PATIENT THAN TO ENGAGE IN RESEARCH WITH UNKNOWN OUTCOMES AND POSSIBLE ADVERSE OUTCOMES.

AND FINALLY, AS DR. DOBKIN DISCUSSED YESTERDAY, MODES OF REHABILITATION ARE ALTERNATIVES TO PARTICIPATION IN SOME RESEARCH. SO AS YOU CAN SEE, THERE ARE MANY ASPECTS OF INFORMATION THAT ARE CONVEYED TO SUBJECTS AND ARE THE RESPONSIBILITY OF THE IRB TO MAKE SURE THAT THEY'RE CONVEYED

THOUGHTFULLY, SENSITIVELY, ACCURATELY, AND IN A LANGUAGE THAT'S UNDERSTANDABLE TO ALL OF THE SUBJECTS.

IN THIS WAY MANY IRB'S ARE INCORPORATING VIDEOTAPE, AUDIO RECORDINGS, PICTURES, DIAGRAMS AND CHARTS IN CONSENT FORMS AND REDUCING THE AMOUNT OF NARRATIVE IN ORDER TO ACCOMMODATE A POPULATION THAT IS ABLE TO READ AND COMPREHEND LESS AND LESS.

INJURY FROM RESEARCH, WELL, YOU KNOW, ONE OF THE OUTCOMES OF RESEARCH COULD BE THAT YOU'RE GOING TO GET HURT. IRB'S ARE ALSO ENTRUSTED WITH ENGAGING THIS PROCESS. THE FEDERAL REGULATIONS, THOUGH, ARE AMBIVALENT ABOUT INJURY IN THAT THERE'S NO REQUIREMENT TO PAY FOR RESEARCH-RELATED INJURIES. NOW, A CONSENT FORM, WE KNOW YOU MUST INFORM SUBJECTS WHETHER THERE IS ANY COMPENSATION AND HOW YOU ARE GOING TO ACCESS MEDICAL TREATMENT, BUT IT DOESN'T SAY WHO HAS TO PROVIDE IT OR WHO HAS TO PAY FOR IT. IN FACT, SOME INSTITUTIONS SAY THAT THE PATIENT PARTICIPATES AT HIS OR HER OWN RISK, PHYSICAL AND ECONOMIC.

CIRM HAS NO SPECIFIC REQUIREMENTS ABOUT INJURY TO SUBJECTS RECEIVING A TEST ARTICLE EITHER. ALTHOUGH CIRM REGULATIONS DO REFERENCE THE FEDERAL REGULATIONS FOR THOSE INSTITUTIONS THAT HOLD AN HHS

ASSURANCE OF COMPLIANCE, BUT THEN IT CIRCLES BACK TO THE TOP IN THE FEDERAL REGULATIONS, WHICH IS THERE ARE NO REQUIREMENTS TO PROTECT SUBJECTS WHO ARE INJURED IN TERMS OF WHAT ARE THE OBLIGATIONS OF THE INSTITUTIONS AND CIRM AS A SPONSOR. ALTHOUGH I SHOULD ADD THAT THERE ARE MANY REQUIREMENTS FOR OOCYTE DONORS AND THEIR PROTECTION.

SO, AGAIN, AN EXAMPLE OF WHERE WE HAVE GONE AND WHERE WE HAVE COME FROM ADDRESSES ONE SET OF RESEARCH CIRCUMSTANCES, BUT IT IS NOT FORWARD LOOKING IN TERMS OF WHERE WE'RE GOING WITH CLINICAL RESEARCH.

FINALLY, BEFORE YOU GO CHECK OUT, INVESTIGATOR CONFLICT OF INTEREST. HOW SHOULD IRB'S AND INSTITUTIONS AND CIRM ADDRESS THE MANAGEMENT OF INVESTIGATOR CONFLICTS WHEN THE INVESTIGATOR IS ALSO THE INVENTOR AND MAY BE THE ONLY PERSON WHO'S EVER ACTUALLY USED THE PRODUCT IN A SETTING THAT COULD BE TRANSLATABLE TO HUMANS? I'LL GIVE YOU AN EXAMPLE.

A SURGEON WHO DEVELOPS A TEST ARTICLE, DRUG OR DEVICE, HAS BEEN THE ONLY PERSON TO DO THE SURGICAL PROCEDURES ON THE ANIMAL MODEL AND IS NOW GOING TO TRANSLATE THAT INTO HUMANS, WILL BE THE PRINCIPAL INVESTIGATOR OF THE RESEARCH, THE INVENTOR AND DISCOVERER, AND MAY ACTUALLY EVEN HAVE AN

ECONOMIC INTEREST IN THE PRODUCTS BEING TESTED.

SHOULD THAT PERSON BE CONDUCTING THE RESEARCH? SHOULD THAT PERSON BE OBTAINING INFORMED CONSENT FROM SUBJECTS? WHO ELSE WOULD BE QUALIFIED TO DO THE RESEARCH? ARE WE PUTTING SUBJECTS AT INCREASED RISK BY SAYING THE PERSON CAN'T DO IT? HOW DO WE MANAGE THESE CONFLICTS? WHO SHOULD BE MANAGING THEM? I CAN TELL YOU AT MANY INSTITUTIONS IT'S THE IRB THAT'S LEFT TO MANAGE THESE CONFLICTS BECAUSE THEIR INSTITUTIONAL CONFLICT OF INTEREST COMMITTEES AREN'T PREPARED TO ANSWER THESE CLINICAL RESEARCH QUESTIONS.

THERE ARE NO CONFLICT OF INTEREST REGULATIONS FROM FDA OR HHS REGARDING WHEN THE INVESTIGATOR IS ALSO THE INVENTOR AND WHAT SHOULD OCCUR. AND CIRM HAS NO REGULATIONS EITHER. ISSCR ACKNOWLEDGES THAT THE NOVEL RESEARCH MAY REQUIRE INVESTIGATORS TO ASSIST IN THE DESIGN, DEVELOPMENT, AND MANUFACTURING PROCESS, AND ASSAYS, BUT, AGAIN, IT'S SILENT ON WHAT SHOULD BE DONE TO MANAGE SUCH CONFLICTS.

SO I'M GOING TO END HERE WITH POSTAPPROVAL MONITORING, AND WE CAN RECONVENE. IS THAT OKAY, BERNIE?

CHAIRMAN LO: THAT SOUNDS GREAT. LET'S

TAKE ANY COMMENTS AND QUESTIONS ON WHAT STEVE SAID SO FAR AND COME BACK LATER.

DR. ROBERTS: WELL, I HAVE A LOT ACTUALLY, SO I'LL TRY NOT TO -- I JUST -- WHAT YOU SAID, I THOUGHT, RAISED A LOT OF ISSUES THAT RELATED TO WHAT WE'VE BEEN TALKING ABOUT. ONE WAS WHAT SEEMS TO BE ATTENTION ABOUT WHO SHOULD BE THE FIRST HUMAN SUBJECT. SHOULD IT BE THE SICKEST OR THE LEAST SICK? AND I THINK WE'VE BEEN GOING ALONG THINKING IT SHOULD BE THE SICKEST. AND, IN FACT, DR. KALICHMAN SUGGESTED THAT, BUT THEY'RE ALSO THE MOST LIKELY TO HAVE THE THERAPEUTIC MISCONCEPTION. THEY'RE THE MOST VULNERABLE. AND YESTERDAY WE ALSO MENTIONED THAT THEY MAY BE THE LEAST LIKELY TO PARTICIPATE IN RESEARCH THAT INVOLVES SHAM SURGERIES.

SO THERE'S A TENSION THERE, I THINK. ALSO, EXPLAINING THE NEED TO EXPLAIN THE RISKS AND CONTINUING REVIEW, WHICH I KNOW YOU'LL GET TO, SEEMS TO ME THAT THAT MIGHT PROVIDE A REASON FOR INSISTING ON CIRM-FUNDED SCIENTISTS TO PUBLISH NEGATIVE FINDINGS. SO THAT I THINK MANY OF US OR SEVERAL OF US HAVE THOUGHT THAT THAT'S A GOOD IDEA AND THIS MIGHT BE AN ADDITIONAL REASON FOR IT BECAUSE, OF COURSE, THOSE NEGATIVE FINDINGS ARE WHAT REVEAL THE

RISKS OF CONTINUING RESEARCH OR RESEARCH OR RELATED RESEARCH BY OTHERS.

AND THEN I ALSO THOUGHT YOU EMPHASIZED THE IMPORTANCE OF RESEARCHERS BEING PART OF THE INFORMED CONSENT PROCESS. AND IN SHAM SURGERIES THAT IT WOULDN'T BE ENOUGH TO HAVE A SHAM SURGERY THAT JUST CONVINCED THE PARTICIPANT THAT SHE WAS GETTING THE ACTIVE ARTICLE, BUT THE RESEARCHERS WOULD HAVE TO BE CONVINCED AS WELL BECAUSE THEY'RE GOING TO BE TREATING THE PATIENTS DIFFERENTLY IF THEY KNOW THAT -- PATIENT IS THE WRONG WORD, BUT THE SUBJECT DIFFERENTLY. SO THAT COMPLICATES THE REQUIREMENTS FOR SHAM SURGERIES.

AND THEN FINALLY, WHEN YOU MENTION DIVERSITY AND YOU RAISE ISSUES ABOUT DIFFERENT CULTURES AND ETHICS AND ALSO JUST THE ABILITY TO READ, THERE'S ALSO, I THOUGHT, AN ASPECT OF DIVERSITY IS ECONOMICS, INCOME. AND THIS RELATES TO WHAT YOU WERE SAYING AT THE END ABOUT WHETHER CIRM SHOULD PROVIDE CARE FOR RESEARCH SUBJECTS WHO REQUIRE CARE FOR RESEARCH SUBJECTS WHO ARE HARMED. THOSE SUBJECTS WHO HAVE NO HEALTH INSURANCE OR CAN'T AFFORD CARE ARE GOING TO BE AT A DISADVANTAGE COMPARED TO WEALTHIER RESEARCH SUBJECTS.

AND ALSO WITH REHABILITATION. YESTERDAY,

DR. DOBKIN, YOU MENTIONED THIS, MENTIONED THAT RESEARCH SUBJECTS SHOULD FIRST ALL BE PROVIDED WITH EXCELLENT REHABILITATION TO MAKE SURE THAT THEY'RE ALL, BOTH THE CONTROL GROUP AND THE TEST GROUP, ARE ABLE TO OPERATE AT THEIR FULLEST CAPACITY. AND ALSO SUGGESTED THAT THAT'S NOT GOING ON NOW. AND I NOTED ALSO IN HIS ARTICLE YESTERDAY -- THE ARTICLE HE MENTIONED YESTERDAY ABOUT CHINA, THAT THE REASON WHY THOSE SUBJECTS, MOST OF THE SUBJECTS, THE ONES WHO IMPROVED, THE REASON WHY THEY IMPROVED WAS THE POSTOPERATIVE CARE THAT THEY GOT, WHICH SUGGESTS THAT AN IMPORTANT ELEMENT OF ALL OF THIS IS THE PRETESTING CARE THAT PATIENTS GET. AND THAT COSTS MONEY TOO. SO THOSE WHO HAVE GOOD HEALTH INSURANCE, HAVE GOOD CARE, ARE WEALTHIER ARE GOING TO BE IN A DIFFERENT POSITION FROM POORER RESEARCH SUBJECTS WHO PERHAPS HAVEN'T GOTTEN ANY CARE.

I KNOW THIS IS A LOT OF THINGS, BUT I REALLY THOUGHT THAT YOUR PRESENTATION BROUGHT IN A LOT OF ISSUES WE'VE BEEN TALKING ABOUT THE LAST COUPLE DAYS THAT I THINK WE NEED TO ADDRESS ALL OF THESE ISSUES. AND I DON'T KNOW IF WE HAVE TIME FOR YOU TO ANSWER ALL OF THEM.

DR. PECKMAN: LET ME TRY TO HIT A FEW POINTS. IN TERMS OF BRINGING ALL THE SUBJECTS TO A

SIMILAR BASELINE, I THINK THAT THE CHALLENGE IS GOING TO BE DIFFERENT DEPENDING ON THE DISEASE AND THE POPULATION. AND THAT WHERE WE'RE DEALING WITH SPINAL CORD INJURY OR PARKINSON'S OR ALZHEIMER'S, YOU'RE GOING TO HAVE DIFFERENT KIND OF SETTING OF A PATIENT POPULATION THAN YOU ARE IN OTHER KINDS OF DISEASES OR DISORDERS, SUCH AS HIV OR DIABETES OR CANCER.

THAT BEING SAID, AND SINCE CIRM IS PLAYING A DUAL ROLE OF CREATING AND SIMILAR TO NIH IN TERMS OF REVIEWING RESEARCH AND CREATING REGULATIONS FOR RESEARCH, YOU'RE IN A UNIQUE POSITION TO ENSURE THAT SOME OF THESE QUESTIONS HAVE AT LEAST A FRAMEWORK IN WHICH TO BE ANSWERED. AND SO, FOR EXAMPLE, WHEN A SCIENTIFIC REVIEW COMMITTEE REVIEWS A PROJECT, IS IT ADDRESSING SOME OF THESE QUESTIONS? THE IRB CLEARLY IS GOING TO HAVE TO ADDRESS THOSE QUESTIONS TO ENSURE EQUITABLE SELECTION, TO ENSURE RISK-BENEFIT CALCULATION. BY THE TIME IT GETS TO THE IRB, IT MAY BE TOO LATE.

DR. ROBERTS: RIGHT.

DR. PECKMAN: AND SO IT'S INCUMBENT UPON THE RFA PROCESS AND THE SCIENTIFIC REVIEW THAT HAPPENS DURING THE RFA PROCESS TO INCLUDE THESE KINDS OF ELEMENTS IN IT.

DR. ROBERTS: UH-HUH.

DR. PECKMAN: IN TERMS OF INJURY, THAT'S GOING TO TACKLE A QUESTION THAT MANY PEOPLE SAY IS ABOVE MY PAY GRADE; HOWEVER, I THINK IT'S INCUMBENT UPON CIRM TO TRY TO THINK ABOUT IT BECAUSE AS WE DEAL WITH NOVEL TEST ARTICLES, THE FIRST TIME IN HUMANS, WITH THE POTENTIAL FOR SERIOUS INJURY. FOR EXAMPLE, IN SPINAL CORD INJURY, I DON'T KNOW IF THIS IS PART OF THE IND THAT GERON HAS FILED AND WHETHER THEY'VE DONE SOMETHING TO MITIGATE THIS, BUT IS IT POSSIBLE THAT THE CELLS WILL PROLIFERATE OUTSIDE THE INTENDED SITE? WELL, YOU HAVE NEURAL CELLS FLOATING THROUGHOUT THE BODY. IF YOU DO, DOES THAT RESULT IN TOTAL INTRACTABLE PERMANENT BODY PAIN? SO ARE YOU CREATING A LARGER DISABILITY FOR SOMEONE WHO'S ALREADY AT A DEFICIT --

DR. ROBERTS: UH-HUH.

DR. PECKMAN: -- WHO'S DOING THIS OUT OF THEIR ALTRUISM AND CERTAINLY NOT TO TAKE AWAY THEIR HOPE AS WELL. SO THESE ARE QUESTIONS THAT CERTAINLY NEED TO BE ANSWERED.

DR. ROBERTS: UH-HUH.

DR. PECKMAN: IN TERMS OF THE DIVERSITY OF THE SUBJECT POPULATION, ECONOMICS, THEIR ACCESS TO HEALTHCARE IN THEIR NONRESEARCH LIFE --

DR. ROBERTS: RIGHT.

DR. PECKMAN: -- ARE ALL IMPORTANT ASPECTS AND PART OF THE CALCULATION THAT SHOULD BE CONSIDERED BOTH PRE-IRB REVIEW AND DURING THE IRB REVIEW.

I'M SORRY. I FORGOT YOUR FIRST ONE.

DR. ROBERTS: MAYBE WE CAN GET TO THIS LATER, BUT JUST ARE THE APPROPRIATE SUBJECTS THE SICKEST OR THE LEAST SICK?

DR. PECKMAN: RIGHT. RIGHT.

DR. ROBERTS: I'VE HEARD ARGUMENTS GOING BOTH WAYS.

DR. PECKMAN: I THINK IT'S GOING TO DEPEND ON THE DISEASE YOU'RE LOOKING AT OR DISABILITY YOU'RE LOOKING AT. IT'S GOING TO DEPEND ON THE TYPE OF RESEARCH THAT YOU'RE PROPOSING AND WHAT ITS TARGET IS. I THINK THERE ARE A LOT OF DIFFERENT VARIABLES THAT ARE GOING TO COME INTO PLAY. AND AGAIN, IT COMES OUT THROUGH THE RFA AND SCIENTIFIC REVIEW PROCESS AND THEN ULTIMATELY TO BE DETERMINED BY THE IRB WHETHER THESE ARE APPROPRIATE PEOPLE TO PLACE AT RISK AT THIS TIME IN THE DEVELOPMENT OF THIS PROJECT.

AND TELL YOU THE TRUTH, I SEE IT HAPPEN ON A DAY-TO-DAY, PROJECT-BY-PROJECT BASIS, AND

SOMETIMES ON A SUBJECT-BY-SUBJECT BASIS. I'VE SEEN IRB'S, FOR EXAMPLE, WHERE THERE ARE SERIOUS ADVERSE EVENTS IN A PROJECT WHERE THE PROJECT GETS SLOWED DOWN TO A SUBJECT-BY-SUBJECT DEFINING OF CONTINUATION DEPENDING ON CERTAIN RESPONSES TO CERTAIN TYPES OF TESTS FOR DRUG DETECTION.

AND I'M GOING TO GET INTO THIS WHEN I TALK ABOUT MONITORING. SO I THINK THAT THERE ARE FRAMEWORKS IN PLACE TO BE USED TO ANSWER ALL THOSE QUESTIONS. THE CHALLENGE TO US IS WILL WE USE THEM? AND WILL WE BE SUCCESSFUL IN ANSWERING THEM?

DR. ROBERTS: THANK YOU.

CHAIRMAN LO: OTHER QUESTIONS OR COMMENTS?

DR. ROBERTS: I THINK DR. KALICHMAN.

DR. KALICHMAN: IF I COULD JUST FOLLOW UP. I AGREE GREATLY WITH STEVE'S POINT THAT THIS SHOULD BE DONE ON A CASE-BY-CASE BASIS IN TERMS OF WHICH PATIENTS. BUT I THINK THE POINT I WAS TRYING TO MAKE OR I KNOW THE POINT I WAS TRYING TO MAKE IS THAT WHEN WE FIRST START THESE TRIALS, THE FIRST HANDFUL, BECAUSE WE ARE ENTERING SUCH NEW TERRITORY WITH THIS PARTICULAR KIND OF TREATMENT, THAT THOSE SHOULD BE IN THAT GROUP OF PATIENTS. I WOULD STRONGLY ARGUE AGAINST MAKING OUR FIRST CHOICE TO TREAT YOUNG PEOPLE FOR SOMETHING THAT MIGHT PROTECT

THEM AGAINST ALZHEIMER'S DISEASE LATER BY PUTTING EMBRYONIC STEM CELLS IN THEIR BRAINS. SO THAT'S THE DISTINCTION.

DR. ROBERTS: RIGHT. I UNDERSTAND.

DR. PECKMAN: BUT A DISEASE THAT IMPACTS ON PEOPLE THAT COULD KILL THEM BEFORE THEY BECOME ADOLESCENTS MAY BE AN APPROPRIATE SUBJECT POPULATION, RIGHT? I MEAN YOU HAVE TO LOOK AT THIS IN A VERY CONTEXTUALIZED WAY. OTHERWISE YOU RUN THE RISK OF OMITTING SOMETHING THAT MAY ACTUALLY HELP US EITHER IN TERMS OF DIRECTLY TO PEOPLE EVENTUALLY OR AT LEAST IN TERMS OF OUR KNOWLEDGE AS TO WHAT CAN OR CAN'T BE DONE IN A SPECIFIC AREA.

CHAIRMAN LO: JEFF.

MR. SHEEHY: I DO WANT TO ECHO DOROTHY'S POINT ABOUT HAVING TO DEAL WITH MEDICAL CARE. BECAUSE I THINK, AS YOU KNOW, BERNIE, IT'S NOT UNCOMMON. I MEAN I'VE HEARD OF EXAMPLES OF PEOPLE WHO BASICALLY GO FROM A RESEARCH SETTING TO SAN FRANCISCO GENERAL BECAUSE THE RESEARCH DOESN'T COVER, SO THEY END UP BEING COVERED BY THE COUNTY OR THE STATE, WHICH I THINK, AT LEAST IN THE SITUATION OF HIV MEDICINE, IS NOT QUITE THE SAME THING AS WHAT WE MIGHT BE TALKING ABOUT WITH SOME OF THE IRREVERSIBLE EFFECTS THAT WE MIGHT SEE IN A REAL

ROBUST SYSTEM OF CARE THAT'S FUNDED BY THE FEDERAL GOVERNMENT AND THE STATE GOVERNMENT AT A LOCAL LEVEL.

SO, YOU KNOW, I DO THINK THAT THERE'S A REAL CONCERN ABOUT PEOPLE GETTING PROCEDURES THAT DO HAVE THESE IRREVERSIBLE EFFECTS AND THEN WHO'S REALLY GOING TO BE RESPONSIBLE? WILL THEIR OWN INSURANCE COMPANIES BE WILLING TO COVER ENDLESS CARE FOR SOMEONE WHO HAS TAKEN A RATHER DRAMATIC -- NEEDS MUCH MORE EXTENSIVE CARE AS A RESULT OF HAVING PARTICIPATED IN A RESEARCH PROJECT? SO I DON'T KNOW HOW WE RESOLVE IT. I THINK IT'S SOMETHING THAT EXISTS AND A LARGER RESEARCH ISSUE. AND WE DO HAVE A GOOD PUBLIC HEALTH SYSTEM IN CALIFORNIA THROUGH MEDI-CAL, BUT I DON'T KNOW -- THERE MAY BE A GAP THERE.

DR. PECKMAN: LET ME ADD A COUPLE AMENDMENTS. ONE IS THAT THE UNIVERSITY OF CALIFORNIA AS A MATTER OF POLICY REQUIRES THAT ALL INDUSTRY-SPONSORED RESEARCH COVER FULL RESEARCH INJURY. SO AS FAR AS THAT GOES, THE UNIVERSITY OF CALIFORNIA IS A CARVE-OUT FOR THIS QUESTION REGARDING COMMERCIAL RESEARCH. SO IF GERON OR AMGEN OR SOME OTHER COMPANY COMES AND SAYS WE WANT TO TRY THIS NEW CELL THERAPY, CELL RESEARCH PROJECT, AND

UNIVERSITY OF CALIFORNIA REQUIRES THE CONTRACT TO INCLUDE THAT THE SPONSOR PAY FOR ANY RESEARCH-RELATED INJURY. THE UNIVERSITY WILL PROVIDE CARE AND WILL BE REIMBURSED BY THE SPONSOR OR SOMEONE ELSE COULD PROVIDE CARE.

NOW, OF COURSE, THAT LEAVES OUT THAT OTHER ASPECTS OF POTENTIAL CIRM-FUNDED INVESTIGATIONS, BUT THAT'S ONE AREA WHERE IT'S DONE. I SHOULD ALSO ADD THAT THE FEDERAL GOVERNMENT HAS NEVER SUCCESSFULLY ADDRESSED THIS QUESTION. AND THEY'VE LEFT IT TO INSTITUTIONS TO HANDLE ON IT A CASE-BY-CASE BASIS, WHICH THAT IN ITSELF MAY BE A QUESTION THAT NEEDS TO BE ADDRESSED IN A LARGER CONTEXT. BUT THE LARGER CONTEXT IS THAT IN THIS COUNTRY WE DON'T HAVE NATIONALIZED HEALTHCARE, AND EVERYONE KIND OF GETS IT AS THEY CAN.

DR. TAYLOR: STEVE, HOW LONG HAS THAT CALIFORNIA POLICY BEEN IN PLACE?

DR. PECKMAN: UNIVERSITY OF CALIFORNIA POLICY HAS BEEN IN PLACE SINCE, I THINK, AT LEAST 1994. I THINK IT'S AT LEAST SINCE 1994.

CHAIRMAN LO: WE HAVE A NUMBER OF QUESTIONS. FRANCISCO. THEN ALTA.

DR. PRIETO: JUST A COUPLE THINGS THAT THIS SORT OF REMINDS ME OF. ONE IS THAT EVERY WEEK

MY LOCAL NEWSPAPER, AND I IMAGINE DOWN HERE ALSO, I SEE ADS FOR PHASE III CLINICAL TRIALS WITH INDUCEMENTS, INCLUDING FINANCIAL INCENTIVES AND ALL MEDICAL CARE PROVIDED DURING THE COURSE OF THE STUDY, BUT I AM ALMOST CERTAIN THAT THERE IS NO COVERAGE AFTER THAT.

DR. PECKMAN: ALL MEDICAL CARE TYPICALLY REFERS TO THE CARE PROVIDED FOR WHATEVER IT IS THEY'RE RESEARCHING OR THE DISEASE YOU MAY HAVE. IT DOESN'T NECESSARILY RESPOND TO ANYTHING THAT MAY RESULT FROM AN INJURY.

DR. PRIETO: NO. YOU GET EXAMINATIONS BY A DOCTOR AND SO ON DURING THE COURSE OF THE STUDY. BUT THE OTHER THING THAT STRIKES ME IS HOW MUCH OF THIS REALLY -- SOME OF THESE VERY BASIC QUESTIONS ARE THINGS THAT YOU DEAL WITH EVERY DAY IN PRIMARY CARE MEDICINE TOO IN JUST PRESENTING A TREATMENT TO A PATIENT. YOU KNOW, I HAVE TO TELL PEOPLE THAT THIS TREATMENT FOR THIS DISEASE THAT I'M PROPOSING TO YOU MAY MAKE YOU BETTER, BUT IT COULD MAKE YOU WORSE. IT COULD MAKE YOU WORSE IN UNEXPECTED WAYS. THESE ARE THE RELATIVE LIKELIHOODS OF THAT AS BEST I KNOW THEM, AND THAT INFORMATION IS OFTEN USUALLY INCOMPLETE. AND THERE'S A WHOLE LITERATURE ABOUT, AT LEAST IN PRIMARY CARE, ABOUT THAT, YOU KNOW,

INFORMING PATIENT EDUCATION AND INFORMED CONSENT IN THAT TYPE OF SETTING. MAYBE YOU CAN LEARN SOMETHING FROM THAT.

DR. PECKMAN: THERE IS A WHOLE LITERATURE IN RESEARCH AS WELL, AND I'D SAY THAT THERE IS ALWAYS CONCERNS AND CALLS FOR IMPROVEMENT THAT, IN GENERAL, INFORMATION IS BEING CONVEYED AND THAT IRB'S HAVE SUCCESSFULLY BEEN DOING THIS JOB FOR DECADES. AND SO THAT'S WHY MY FIRST QUESTION IN THE SECOND SLIDE WAS THE INTENT TO REINVENT THE WHEEL AND IS IT ACTUALLY NECESSARY.

DR. PRIETO: WELL, I THINK VARYING DEGREES OF SUCCESS BECAUSE SOME OF THE CONSENT THAT'S OBTAINED I HAVE BIG CONCERNS ABOUT. I MEAN PEOPLE SIGN A FORM AND THAT FORM INCLUDES ALL THAT INFORMATION, BUT REALLY IN A WAY IN A FORM THAT'S UNINTELLIGIBLE TO MOST PEOPLE.

DR. PECKMAN: I COULD NEVER DISAGREE WITH THAT. ON THE OTHER HAND, WHEN YOU TAKE IN THE NUMBER OF TENS OF THOUSANDS OF CONSENT FORMS APPROVED BY IRB'S IN THIS COUNTRY, THAT I THINK YOU'D BE HARD-PRESSED TO SAY THE MAJORITY OF THEM FALL IN THAT CATEGORY.

DR. CHARO: I'D LIKE TO GET BACK TO SOMETHING YOU SAID AT THE VERY BEGINNING AND YOU

JUST REITERATED STEVE. AND THAT IS ABOUT NOT REINVENTING THE WHEEL BECAUSE I APPRECIATE VERY MUCH THE KIND OF OVERVIEW THAT YOU GAVE OF THE GENERAL ISSUES, BUT CERTAINLY CIRM IS NOT INTERESTED IN TRYING TO SOLVE THE GENERAL PROBLEMS OF HUMAN SUBJECTS RESEARCH. RIGHT. AND THERE WERE POINTS IN YOUR PRESENTATION WHERE YOU WERE TRYING TO PULL OUT THOSE THINGS THAT ARE EITHER UNIQUE TO STEM CELL CLINICAL TRIALS OR AT LEAST ESPECIALLY DIFFICULT. I MEAN YOU POINTED OUT, FOR EXAMPLE, THE SPECIAL CONFLICT OF INTEREST RULES REGARDING EGG DONATION.

BEING ABLE TO HAVE A KIND OF SYNTHESIZED LIST, I MEAN A QUICK LIST OF THOSE THINGS THAT ARE EITHER UNIQUE OR ESPECIALLY DIFFICULT IN STEM CELL RESEARCH WOULD BE VERY HELPFUL BOTH TO FOCUS OUR ATTENTION TO THOSE THINGS THAT ARE APPROPRIATE FOR CIRM AND ALSO POTENTIALLY TO FOCUS OUR ATTENTION ON SOLUTIONS OTHER THAN BUREAUCRATIC SOLUTIONS.

FOR EXAMPLE, MICHAEL KALICHMAN MADE A POINT EARLY ON THAT SOME OF THESE INTERVENTIONS ARE IRREVERSIBLE, AND THAT POSES A SPECIAL PROBLEM IN MANAGING RISKS. AND YET WE KNOW THAT AT LEAST FOR SOME SUBSET OF THE INTERVENTIONS, THERE ARE PEOPLE ACTIVELY WORKING ON WAYS SPECIFICALLY TO REVERSE THEM. FOR EXAMPLE, BIOENGINEERING THE CELLS BEFORE

TRANSPLANT SO THAT THEY ARE NOT ACTIVE EXCEPT IN THE PRESENCE OF A DRUG THAT CAN PENETRATE THE BLOOD-BRAIN BARRIER AND THEN YOU GIVE THE SUBJECT THE DRUG. AND AS SOON AS YOU SEE THAT THERE'S A PROBLEM OR IT'S SECRETING TOO MUCH, YOU STOP THE DRUG AND NOW THE CELLS ARE NO LONGER FUNCTIONING.

SO HERE, INSTEAD OF IT BEING AN INFORMED CONSENT PROBLEM OR AN IRB PROBLEM, IT'S ACTUALLY A TECHNICAL PROBLEM OF HOW TO SCIENTIFICALLY MANAGE THE RISK. SO --

DR. PECKMAN: IT'S A RISK-BENEFIT QUESTION.

DR. CHARO: BUT IT'S A WAY OF ACTUALLY NOT TRYING TO PUSH IT ALL INTO THE SOCIAL ISSUE OF HOW DO YOU RECRUIT AND HOW DO YOU INFORM, BUT RATHER TO ACTUALLY ASK HOW CAN WE ACTUALLY REDUCE THE RISKS BY FOCUSING OUR SCIENTIFIC RESEARCH AND OUR MEDICAL RESEARCH ON THESE IDENTIFIED AREAS THAT ARE ESPECIALLY TRICKY WITH STEM CELLS. THERE'S NO QUESTION HERE SO MUCH AS JUST AN OBSERVATION BECAUSE I FEAR THAT WE MAY VEER OFF INTO A LAND THAT GOES BEYOND THE MANDATE OF CIRM OR OF THIS PARTICULAR SUBCOMMITTEE IF WE'RE NOT CAREFUL OURSELVES BECAUSE ALL THESE ISSUES ARE VERY INTERESTING.

DR. PECKMAN: I THINK THERE ARE TWO POINTS

I HOPE YOU LEAVE WITH BEFORE YOU GO CHECK OUT OF THE HOTEL. ONE IS THAT IT'S REALLY UNNECESSARY TO REINVENT THE WHEEL THOUGH IT MAY BE HELPFUL TO OPTIMIZE THE WHEEL, GREASE THE WHEEL.

TWO IS THAT THERE'S A RISK-BENEFIT ANALYSIS THAT NEEDS TO TAKE PLACE AT ALL STEPS. AND CLEARLY, AS ALTA WAS OUTLINING, IT IS POSSIBLE TO SCIENTIFICALLY MINIMIZE RISK. AND THAT'S WHERE WE SHOULD START. BECAUSE TO DO IT POSTFACTO ISN'T GOING TO BE VERY HELPFUL. AND ALL THE STUFF I'M GOING TO GET INTO AFTER THE BREAK IS ALL GOING TO HAPPEN AFTERWARDS. AND SO THE IDEA THAT WE CAN CREATE SOME KIND OF KILLER CELL OR A DRUG THAT WILL TURN OVER THE CELL, WHICH A LOT OF PEOPLE ARE DOING.

IN FACT, THERE ARE MANY INSTITUTIONS ACROSS THE COUNTRY AND IN THIS WORLD WHO ARE DEALING WITH IMMUNITY PROTOCOLS WHERE THEY'RE GOING TO MODIFY GENETICALLY SOME CELLS. THEY'RE GOING TO GIVE IT TO PEOPLE, AND THROUGH MONITORING THROUGH THINGS LIKE PET SCAN, THEY IDENTIFY METABOLIC CHANGES HAPPENING. THEY HAVE A PROCESS IN WHICH THEY CAN STOP THE CELL. THERE WE'VE TOTALLY MINIMIZED THE RISK OF X, THOUGH THERE MAY BE SMALL RISKS OF Y AND Z THAT GO BEFORE X OCCURS. SO THIS IS ALL PART OF THE SCIENTIFIC PROCESS THAT HAS TO

HAPPEN PRIOR TO THE POINT WHERE A PROJECT IS APPROVED FOR THE ENROLLMENT OF SUBJECTS.

CHAIRMAN LO: JEFF, LAST COMMENT.

MR. SHEEHY: WELL, TWO. ONE AGAIN THINKING ABOUT THIS MEDICAL CARE, IF WE DO IMPROVE THE STANDARD OF CARE, AND IT MAY ACTUALLY BE NECESSARY, AT LEAST TALKING ABOUT THE TYPES OF INTERVENTIONS THAT DR. DOBKIN WAS TALKING ABOUT YESTERDAY IN ORDER TO HAVE PEOPLE SUCCEED OR HAVE A REASONABLE CHANCE OF SUCCESS, WE'VE INDUCED PEOPLE TO ENTER INTO THE TRIAL. IF PART OF BEING IN THIS TRIAL -- AND WHEN YOU DESCRIBE A POPULATION THAT MAY NOT HAVE ACCESS TO GOOD HEALTHCARE, IN SOME PARTS OF CALIFORNIA THE ACTUAL PATIENT POPULATION WE'RE TRYING TO ADDRESS AS A CONTEXT FOR BEING ABLE TO EVEN SUCCEED IN THIS TRIAL, YOU HAVE TO HAVE A DRAMATICALLY IMPROVED STANDARD OF CARE, THEN YOU'VE JUST BEEN INDUCED TO PARTICIPATE IN THIS TRIAL.

THAT'S SOMETHING WE'VE SEEN IN TRIALS IN THE DEVELOPING WORLD WHERE PEOPLE BASICALLY COME INTO A TRIAL SIMPLY BECAUSE THAT'S THEIR ONLY ACCESS TO HEALTHCARE, AND SO THEY'RE HAPPY TO PARTICIPATE.

THE SECOND PROBLEM -- THE SECOND QUESTION I HAVE IS IN TERMS OF REINVENTING THE WHEEL. IRB'S SEEM TO BE THE REAL BACKBONE. WHAT ABOUT WHEN IRB'S

HAD DIFFERENT STANDARDS? YOU KNOW, GENE THERAPY TRIALS FOR HIV. YOU AT UCLA HAD A DIFFERENT STANDARD FOR INCLUSION THAN AT UCSF, AND WE ONLY TOOK PEOPLE WHO WERE IN SALVAGE THERAPY. THAT MAY HAVE CHANGED. WE MAY HAVE EASED. AND YOU TOOK PEOPLE WHO ARE RELATIVELY HEALTHY. IS THAT A GOOD THING? IS THAT A BAD THING? DO WE MIND DIVERSITY? DO WE WANT TO MAKE THEM UNIFORM? I MEAN I CAN ARGUE EITHER WAY ON THAT POINT.

DR. PECKMAN: YOU MADE THE POINT. YOU CAN ARGUE IT EITHER WAY. AND CERTAINLY WELL-INFORMED, KNOWLEDGEABLE, AND THOUGHTFUL IRB'S MAY COME TO DIFFERENT CONCLUSIONS. BECAUSE THEY'RE DIFFERENT CONCLUSIONS DOESN'T NECESSARILY MEAN THEY'RE WRONG ON EITHER SIDE.

THAT BEING SAID, IT MAY BE AN OPPORTUNITY TO THINK ABOUT THE SCIENCE OF THE PROTOCOL AND HOW IT'S STRUCTURED BECAUSE IF IT IS DEEMED APPROPRIATE THAT THERE BE MORE RESTRICTED INCLUSION, THEN IT SEEMS LIKE THAT A UNIFORM PROTOCOL WOULD BE THE CALL OF THE DAY.

MR. SHEEHY: WE'RE GOING TO BE DEALING WITH MUCH MORE COMPLEX THINGS THAN HIV MEDICINE, AND IT'S JUST DIFFERENT PERCEPTIONS OF RISK.

DR. PECKMAN: WELL, WE'LL BE DEALING WITH

HIV MEDICINE IN A CELL TECHNOLOGY FORM.

MR. SHEEHY: I MEAN SOME OF THESE OTHER DISEASES, I MEAN IT REALLY IS A PERCEPTION OF RISK. IS THAT OKAY THAT WE HAVE DIFFERENT PERCEPTIONS OF RISK AT TWO VERY RESPECTABLE INSTITUTIONS? WE'RE NOT TALKING ABOUT WHAT MAY BE A LITTLE COWBOY ON THE INDUSTRY SIDE. WE PRAY THAT THOSE IRB'S ARE GOOD.

DR. PECKMAN: WE'RE NOT TALKING ABOUT COWBOYS. WHAT WE'RE TALKING ABOUT IS THE FLEXIBILITY WITHIN A RESEARCH DESIGN THAT ALLOWS FOR THAT BROAD SPECTRUM OF INCLUSION. MY QUESTION IN RESPONSE TO THAT IS IS THAT AN APPROPRIATE DESIGN?

MR. SHESTACK: IN THE VERY BEGINNING WHEN YOU WERE TALKING ABOUT YOUR IRB MAKEUP, YOU DIDN'T MENTION IS IT TYPICAL TO HAVE STAKEHOLDERS WHO AREN'T NECESSARILY MEDICAL EXPERTS ON IRB PANELS?

DR. PECKMAN: YES. IRB IS REQUIRED TO HAVE A MINIMUM OF FIVE PEOPLE, THIS IS FEDERAL REGULATIONS, THEY HAVE TO HAVE PEOPLE WITH SUFFICIENT SCIENTIFIC EXPERTISE TO EVALUATE THE PROTOCOLS. YOU HAVE TO HAVE AT LEAST ONE NONSCIENTIST, AND YOU HAVE TO HAVE AT LEAST A NONAFFILIATED MEMBER.

MR. SHESTACK: DOESN'T NECESSARILY MEAN A STAKEHOLDER THOUGH.

DR. PECKMAN: NO, IT DOES NOT. I CAN TELL YOU THAT MANY IRB'S DO INCLUDE STAKEHOLDERS.

MR. SHESTACK: I THINK OF IT ONLY -- AND MAYBE SOMETHING WILL NOT COME UP FOR A LONG TIME WITH US, BUT I THINK ABOUT IT ONLY IN TERMS OF VULNERABLE POPULATIONS, PARTICULARLY CHILDREN, PARTICULARLY WHERE THERE HAVE BEEN VAST DIFFERENCES IN IRB APPROACHES AS TO WHAT IS A REASONABLE RISK OR WHAT IS CONSIDERED INVASIVE WHEN ACQUIRING PARTICULARLY NONAFFECTED CHILDREN FOR SOMETHING AS SEEMINGLY BENIGN TO, SAY, A THROAT SWAB FOR A THROAT CULTURE.

AND THEN YOU HAVE A POINT OF VIEW OF PARENTS WHO MAY HAVE A CHILD WHO IS VERY ILL WHO MAY SAY THIS CHILD IS -- YES, THIS CHILD DOES NOT HAVE A LIFE-THREATENING DISEASE, BUT THEY HAVE A LIFE SENTENCE, AND THEY WOULD EXPECT -- THEY WOULD ACCEPT A MUCH HIGHER DEGREE OF RISK THAN SOMEONE WHO DOESN'T HAVE THAT DAY-TO-DAY CARE.

THESE ARE NOT ISSUES WE'RE GOING TO DEAL WITH ACTUALLY IMMEDIATELY LOOKS LIKE ON ANY OF OUR THINGS, BUT IT IS SOMETHING TO THINK ABOUT IN HAVING A BROADER REPRESENTATION OF THOSE KINDS OF STAKEHOLDERS WHEN IT COMES TIME TO MAKE THOSE KINDS OF DECISIONS.

CHAIRMAN LO: OKAY. LET'S TAKE A 15-MINUTE BREAK AND GET CHECKED OUT. SO WE WILL COME BACK -- IT'S ABOUT 11:15 NOW -- LET'S COME BACK AT 11:30. THANKS VERY MUCH, STEVE.

(A RECESS WAS TAKEN.)

CHAIRMAN LO: OKAY. WE'RE GOING TO HAVE A LITTLE MODIFICATION IN THE SCHEDULE. I THINK WE'RE HAVING A TERRIFIC DISCUSSION ON IMPORTANT ISSUES. I'M GOING TO INTERRUPT STEVE'S PRESENTATION AND ASK INSU HYUN TO COME IN AND SPEAK NEXT. HE'S ASSOCIATE PROFESSOR OF BIOETHICS AT CASE WESTERN RESERVE, WHO IS THE CHAIR OF THE ISSCR, INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH ETHICS AND POLICY COMMITTEE. AND HE CO-CHAIRED A RECENT PUBLICATION FROM ISSCR WHICH IS REALLY A SET OF INTERNATIONAL CONSENSUS RECOMMENDATIONS, GUIDELINES, ON THE CONDUCT OF CLINICAL TRIALS WITH STEM CELLS.

SO I'M GOING TO HAVE HIM GO NEXT, AND THEN COME BACK TO STEVE'S, THE REST STEVE'S PRESENTATION A LITTLE BIT LATER. SO INSU, WE'RE TRYING TO GET YOUR SLIDES. OH, HE DOESN'T HAVE SLIDES. HE'S A PHILOSOPHY PROFESSOR AND WILL SPEAK WITHOUT SLIDES. SO THANKS. WE'RE GLAD TO HAVE YOU HERE AND WE'RE GLAD TO GIVE YOU WARM SUNNY WEATHER AS A BREAK FROM CLEVELAND.

DR. HYUN: SO I'M FROM CLEVELAND, AND WHAT I WILL DO TO GET SOME WARM WEATHER.

OKAY. WELL, THANK YOU, EVERYBODY, FOR HAVING ME HERE. I DO LIKE THE ANALOGY OF THE WHEEL AND WHETHER WE NEED TO REINVENT IT OR NOT. MY VIEW IS THAT WE DON'T NEED TO REINVENT THE WHEEL, BUT IT MAY NEED SOME ADDITIONAL SPOKES. I'M A CYCLIST AND WHEN I ADD SPOKES, YOU OBVIOUSLY ADD STRENGTH; BUT IF YOU ADD TOO MANY SPOKES, YOU END UP WOBBLING THE WHEEL AND YOU LOSE CONTROL AND CRASH. SO THE TRICK IS KNOWING HOW MANY SPOKES TO ADD WHERE AND WHETHER WE NEED THESE ADDITIONAL SPOKES.

THERE'S A DIFFICULT BALANCE BETWEEN WANTING TO BE STEM CELL SPECIFIC IN MOVING FORWARD THE POLICY AND AVOIDING WHAT I CALL UNWARRANTED STEM CELL EXCEPTIONALISM. WHEN WE DRAFTED THESE ISSCR GUIDELINES, IT WAS DIFFICULT SOMETIMES TO KNOW WHERE THAT RIGHT BALANCE IS. THIS IS THE PROCESS THAT TOOK 13 MONTHS. THERE WERE COMMITTEE MEMBERS, 30 COMMITTEE MEMBERS, FROM 13 DIFFERENT COUNTRIES, AND THERE WAS A WIDE RANGE OF EXPERTISE REPRESENTED IN THIS GROUP. WE HAD PEOPLE -- WE HAD CLINICIANS, WE HAD TRANSPLANT SPECIALISTS, WE HAD STEM CELL BIOLOGISTS, PEOPLE IN THE REGULATORY BACKGROUND, BIOETHICISTS, PEOPLE WHO HAD EXPERIENCE IN GENE

TRANSFER RESEARCH, AND EVERYBODY BROUGHT THEIR OWN PARTICULAR PERSPECTIVE TO THIS TASK.

AND I CAN'T EMPHASIZE THIS ENOUGH. I DON'T BELIEVE THAT THE GUIDELINES DOCUMENT IS SOLELY THE PRODUCT OF THIS TASK FORCE. THE REASON FOR THAT IS THAT WE HAD A PERIOD OF PUBLIC COMMENT WHERE WE ACTUALLY VERY SPECIFICALLY SENT THE DOCUMENT, THE DRAFT DOCUMENT, TO VARIOUS INTERNATIONAL GROUPS, SUCH AS A GROUP IN AUSTRALIA THAT'S SORT OF THE FDA EQUIVALENT, THE FDA HERE IN THE UNITED STATES, WE SENT IT TO CIRM, WE SENT IT TO LOTS OF VARIOUS PEOPLE INTERNATIONALLY WHO HAVE THEIR OWN REGULATORY OPINIONS TO COME TO BEAR ON IT.

SO THE RESULT OF THIS COLLABORATIVE PROCESS, NOT ONLY WITHIN THE MULTIDISCIPLINARY GROUP THAT MADE UP THE TASK FORCE, BUT TO ASK THE OPINIONS OF PEOPLE ON THE DRAFT DOCUMENT WITH PEOPLE REPRESENTING ALL THESE VARIOUS REGULATORY SCHEMES IN EUROPE, ETC., AND JAPAN. WE ENDED UP WITH A DOCUMENT THAT I THINK REALLY SPEAKS TO WHAT ARE CONSIDERED TO BE THE BEST SORT OF FOUNDATIONAL PRINCIPLES BEFORE WE MOVE FORWARD.

NOW, AFTER AGREEING TO TAKE ON THE ROLE OF CO-CHAIR OF THIS TASK FORCE, IT QUICKLY DAWNED ON ME AND TO THE OTHER MEMBERS OF THE TASK FORCE HOW

ENORMOUS THE TASK WAS. I THINK IF IT DAWNED ON US BEFORE WE AGREED, WE MAY NOT HAVE AGREED TO DO IT. SO WHAT I'M ABOUT TO SAY NOW IS SORT OF SOMETHING THAT I'VE BEEN MULLING OVER ON MY OWN FOR THE LAST FEW MONTHS AFTER WE'VE COMPLETED THE DOCUMENT. AND THIS JUST KIND OF GIVES YOU AN IDEA OF WHAT I THINK ARE THE COMPLEXITIES.

SO IMAGINE IF YOU HAVE THIS ENORMOUS MATRIX OR GRID OF ALL DIFFERENT COMBINATIONS. CELL-BASED THERAPIES IS SORT OF A PLACEHOLDER FOR THIS ENORMOUS GRID. WE HAVE DIFFERENT CELLS OF ORIGIN, WHETHER PLURIPOTENT OR MULTIPOTENT. WE HAVE ONE LEVEL OF DIFFERENCE AS WELL WHICH IS WHETHER THEY'RE GENETICALLY MODIFIED OR MINIMALLY MANIPULATED OR MORE THAN MINIMALLY MANIPULATED. AMONG THE PEOPLE WHO WERE ADVISORS FOR THE TASK FORCE WERE REPRESENTATIVES OF THE FDA. AND ACCORDING TO THE FDA'S BIOLOGIC DIVISION, THEY DEFINE MINIMALLY MANIPULATED CELLS AS CELLS IN NONPROLIFERATING CULTURE CONDITIONS TYPICALLY FOR LESS THAN 48 HOURS.

SO WE HAVE MINIMALLY MANIPULATED, WE HAVE MORE THAN MINIMALLY MANIPULATED, GENETICALLY MODIFIED, WE HAVE A FULL ARRAY FOR EACH OF THESE CELLS OF ORIGIN. AND THEN YOU HAVE THE NEXT LEVEL.

YOU SEE THIS TREE IS BRANCHING OUT AS WE GO FURTHER, FURTHER DOWN ALL THE DIFFERENT POSSIBILITIES. WE HAVE AUTOLOGOUS VERSUS ALLOGENEIC TRANSPLANTATION. AUTOLOGOUS IS YOU GET THE CELLS FROM THE DONOR AND YOU PUT IT BACK INTO THE DONOR USING THE PERSON'S CELLS. ALLOGENEIC IS YOU GET FROM ONE PERSON, PUT IT IN ANOTHER PERSON.

EACH OF THESE COMBINATIONS HAS DIFFERENT RISK ASSESSMENTS. WE ALSO HAVE, THEN, AFTER THAT WHETHER IT'S FOR HOMOLOGOUS USE OR NONHOMOLOGOUS USE. HOMOLOGOUS USE WOULD BE PUTTING THE CELLS BACK INTO THE SYSTEM FROM WHICH THEY WERE DERIVED, AND NONHOMOLOGOUS WOULD BE PUTTING THESE CELLS INTO A SYSTEM THAT'S DIFFERENT FROM THE SYSTEM FROM WHICH THEY WERE DERIVED, LIKE BONE MARROW CELLS TO THE BRAIN WOULD BE NONHOMOLOGOUS.

WE HAVE WHETHER THE ADMINISTRATION OF THE CELLS WOULD BE SYSTEMIC OR WHETHER IT WILL BE LOCALIZED; AND ONCE IT'S LOCALIZED, WHETHER IT WILL BE USED IN COMBINATION WITH A MEDICAL DEVICE, WHICH SOME PROPOSALS HAVE BEEN OUT THERE SUCH AS THE HEART, WHETHER YOU CAN HAVE AN ACTUAL VIOLATION TO YOUR DEVICE. SO ALL THESE CREATE AN ENORMOUS ARRAY OF DIFFERENT POSSIBLE COMBINATIONS, EACH OF THEM INCREASING IN LEVEL OF UNCERTAINTY AND RISK.

SO WHEN WE TALK ABOUT CELL-BASED THERAPIES AND GUIDELINES FOR THE TRANSLATIONAL RESEARCH TO CELL-BASED THERAPIES, WE'RE TALKING ABOUT AN ENORMOUS ARRAY, AN ENORMOUS RANGE OF POSSIBILITIES. SO WE KNEW THAT WE COULDN'T GO THROUGH EACH SINGLE ONE OF THESE. I MEAN WE WOULD END UP WITH A DOCUMENT THAT'S HUNDREDS OF PAGES LONG, AND IT WOULD BE QUICKLY OUTDATED IN THE NEXT FEW MONTHS.

SO WHAT WE HAD TO DO, WHAT WE HAD TO AGREE UPON WAS THAT WE WERE GOING TO JUST HAVE A GENERAL SET OF PRINCIPLES AND IDENTIFY WHAT WE THINK ARE THE STEM CELL ISSUES GOING FORWARD IN THIS FIELD.

NOW, SURPRISINGLY, GIVEN THE PLURALITY OF PEOPLE'S BACKGROUNDS AND ALSO INTERNATIONAL BACKGROUNDS ON THIS COMMITTEE, IT WAS VERY PLEASANTLY SURPRISING TO ME THAT THERE WAS REALLY QUITE A LOT OF AGREEMENT IMMEDIATELY ON MANY OF THESE POINTS. AND THAT WAS A PLEASANT SURPRISE TO ME HAVING WORKED ON SIMILAR TYPES OF COMMITTEES. TYPICALLY YOU GET MIRED DOWN IN SOME REALLY INTRACTABLE DISAGREEMENTS, WHETHER THEY'RE CULTURALLY BASED OR WHATEVER. SO WE SAW VERY LITTLE OF THAT WHICH WAS INTERESTING. AND WHAT WAS INTERESTING, HEARING THE DISCUSSIONS SO FAR TODAY, IS SIMILAR CONCERNS AND THEMES KEPT COMING UP.

SO WHAT I WANT TO RELATE TO YOU NOW IS WHAT I'M HEARING IN THIS ROOM IS VERY SIMILAR TO THE KINDS OF CONCERNS THAT THE INTERNATIONAL TASK FORCE HAD ALSO RAISED. SO THAT'S ENCOURAGING. I'M HEARING SIMILAR CONCERNS, AND IT'S NOT LIKE THE GROUPS WOULD BE COMPLETELY DISPARATE IN TERMS OF WHAT THEIR ORDER OF PRIORITY AND CONCERNS MIGHT BE.

SO THE ONE AREA THAT DID HAVE QUITE A BIT OF LIVELY DISCUSSION AND I THINK IN THE END WE ENDED UP HAVING SOME KIND OF GENERAL AGREEMENT ABOUT WAS WHETHER OR NOT IT WOULD BE APPROPRIATE TO HAVE A STATEMENT SAYING THAT IT'S ACCEPTABLE IN SOME LIMITED CIRCUMSTANCES FOR CELL-BASED INTERVENTIONS TO BE ATTEMPTED OUTSIDE THE CONTEXT OF A CLINICAL TRIAL. SO MEDICAL INNOVATION VERSUS CLINICAL TRIAL. AND THE REASON FOR THAT IS THAT WE HAD PEOPLE ON THE COMMITTEE WHO SAID ON THE ONE HAND YOU WANT EVERYTHING TO GO THROUGH CLINICAL TRIALS. CLINICAL TRIAL IS THE BEST WAY TO PROCEED FORWARD. AND WE HAD OTHERS FROM THE TRANSPLANT COMMUNITY, LET'S SAY, WHO WOULD SAY THINGS LIKE, LOOK, IF WE WEREN'T ALLOWED TO HAVE ANY MEDICAL INNOVATION OUTSIDE THE CONTEXT OF A CLINICAL TRIAL, WE WOULDN'T HAVE A LOT OF THE SURGICAL INNOVATIONS THAT WE HAVE TODAY.

IN FACT, I SAW A RECENT STATISTIC THAT IT

WAS LIKE MORE THAN 50 PERCENT, UP TO LIKE 60, 70 PERCENT OF SURGICAL PRACTICES TODAY DEVELOP OUTSIDE THE CONTEXT OF A CLINICAL TRIAL.

NOW, LET'S GO BACK TO THE MATRIX I TOLD YOU ABOUT. OKAY. SO IT DEPENDS ON WHETHER OR NOT THE CELL-BASED INTERVENTION IS VERY SIMILAR TO A SURGICAL INTERVENTION, LOCAL ADMINISTRATION, AUTOLOGOUS TRANSPLANTATION, ETC., ETC. AND SO I THINK YOU NEED TO BE AWARE THAT EARLY ON IN THE PROCESS, DEPENDING ON WHAT KIND OF CELL-BASED INTERVENTION YOU'RE TALKING ABOUT, IT MAY BE MORE APPROPRIATE TO GO ALONG THE LINES OF SORT OF AN ETHICALLY ROBUST DEVELOPMENT OF MEDICAL INNOVATION VERSUS A CLINICAL TRIAL BECAUSE THERE ARE ADVANTAGES AND DISADVANTAGES TO GOING DOWN EACH TRACK. CLINICAL TRIALS TAKE A LONG TIME. AND THEY'RE PROBABLY NOT AMENABLE TO THE KIND OF CONDITIONS SOME OF YOU HAVE BEEN TALKING ABOUT WHICH WERE THE REAL SEVERE CASES WHERE LIMITED OPTION IS AVAILABLE FOR THE PATIENT.

IF YOU GO DOWN THE CLINICAL TRIALS ROUTE, THE DISADVANTAGE THERE IS, WELL, LIMITED ACCESS. THEN YOU GET INTO ISSUES OF COMPASSIONATE USE, ETC. AND THE PERSON IS PROBABLY NOT GOING TO SURVIVE.

NOW, WHAT'S INTERESTING TO ME ABOUT THE

MEDICAL INNOVATION ROUTE IS THAT THE ETHOS IS VERY DIFFERENT FROM THE INVESTIGATOR IN THE CLINICAL TRIALS ROUTE. BECAUSE IN THE CLINICAL TRIALS ROUTE, YOU HAVE TO HAVE CLINICAL EQUIPOISE GOING FORWARD. BUT IN THE MEDICAL INNOVATION ROUTE, NORMALLY FOR THOSE CASES, THE CLINICIAN BELIEVES IN THEIR HEART OF HEARTS THAT THIS MIGHT HELP THE PATIENT. IN THE MEDICAL INNOVATION ROUTE, THE GOAL IS TO HELP THE PATIENT WHO'S UNDER SOME VERY DESPERATE CIRCUMSTANCES. SO PATIENT CARE IS THE GOAL THERE; WHEREAS, FOR CLINICAL RESEARCH, IT'S MAYBE A SIDE EFFECT OR SORT OF A HAPPY COINCIDENCE IF THAT HAPPENS. BUT THE GOAL THERE IS COMPLETELY DIFFERENT FROM THE GOAL THAT YOU SET FORTH FOR MEDICAL INNOVATION.

SO I ENCOURAGE YOU TO KIND OF BE OPEN TO THINKING WHEN ARE WE ONLY TALKING ABOUT CLINICAL RESEARCH AND WHEN, IF AT ALL, WOULD YOU ALLOW FOR FUNDING FOR RESPONSIBLE MEDICAL INNOVATION. HOW WOULD WE KNOW WHAT CATEGORY TO PUT SOME OF THESE PROPOSALS?

DR. WAGNER: I HAVE ABSOLUTELY NO IDEA, AN EXAMPLE OF SOMETHING THAT WOULD NOT BE CONSIDERED RESEARCH. OR MY INITIAL RESPONSE IS IS THAT, QUOTE, CLINICAL CARE IS NOT REALLY CLINICAL CARE. BUT,

AGAIN, I MIGHT BE MISSING SOMETHING. BUT IN THE CONTEXT OF STEM CELL THERAPIES, I CANNOT THINK OF A SINGLE EXAMPLE THAT WOULD BE OUTSIDE THE CONTEXT OF A CLINICAL TRIAL.

DR. HYUN: OKAY. FINE. WELL, YOU KNOW, THE KIND OF INTERVENTIONS THAT WE HAD IN MIND FOR THE ISSCR DOCUMENT WAS RATHER BROAD. SO WHAT WE TALKED ABOUT IS WHAT THE DOCUMENT COVERS ARE RESEARCH OR INTERVENTION INVOLVING PLURIPOTENT STEM CELLS AND THEIR PRODUCTS, THE USE OF SO-CALLED ADULT OR SOMATIC STEM CELLS IN NOVEL WAYS OR FETAL TISSUE IN NOVEL WAYS, AND THE USE OF HEMATOPOETIC OR OTHER STEM CELLS THAT ARE USED CURRENTLY IN CLINICAL CARE OUTSIDE OF THEIR CLINICAL CARE CONTEXT.

SO I MEAN THIS IS A DEBATE. THIS WAS THE LIVELY DISCUSSION WE WERE HAVING IS COULD THERE EVER BE A CIRCUMSTANCE WHERE SOMEBODY WOULD USE A PLURIPOTENT OR EMBRYONIC STEM CELL-DERIVED PRODUCT AS A MEDICAL INNOVATION? AND I THINK THE GROUP WAS GENERALLY UNDER THE AGREEMENT THAT NO. BUT WHAT ABOUT THE OTHER FORMS, TAKING BLOOD STEM CELLS AND USING THEM IN OTHER WAYS FOR CERTAIN CONDITIONS? SO ALL OF THIS IS GOING TO BE CONTEXT SPECIFIC.

BUT ANYWAY, THE DISCUSSION WAS ON THE TABLE. THAT WAS THE ONE. THAT ISSUE WAS THE ONE IN

WHICH THERE WAS THE MOST FRICTION. BUT WHAT WE ENDED UP DECIDING WAS THAT WE'RE GOING TO HAVE A SEPARATE SECTION OF THE GUIDELINES THAT IS OUTSIDE OF THE CLINICAL RESEARCH ENVIRONMENT AND SAYING IF ONE WERE TO DO MEDICAL INNOVATION OUTSIDE OF A CLINICAL TRIAL, HERE ARE SOME GUIDELINES FOR THAT BECAUSE THERE ARE BAD WAYS TO DO IT AND MAYBE SOME GOOD WAYS TO DO IT, AND HERE'S POSSIBLY A GOOD WAY TO DO IT.

DR. WAGNER: I'M STILL SKEPTICAL. BUT THEN IF IT'S NOT A CLINICAL TRIAL, THEN THE FUNDING SHOULD COME FROM INSURANCE COMPANIES AND SHOULD BE CONSIDERED CONVENTIONAL MEDICAL PRACTICE. SO THEREFORE, IF YOU EVER WISH TO REPORT IT, YOU KNOW, IF NOTHING ELSE BECAUSE MAYBE THERE ARE EXAMPLES, BUT I AM SKEPTICAL, MAYBE THERE ARE EXAMPLES, IN WHICH CASE THEN, IF THERE'S ANY QUESTION WHATSOEVER, THEN IT SHOULD BE JUST AT LEAST REVIEWED WITH THE IRB'S TO DETERMINE WHETHER OR NOT IT'S APPROPRIATE TO BE A CLINICAL TRIAL OR NOT. BUT I JUST CAN'T THINK OF ANY EXAMPLE.

I THINK THAT WHAT YOU'RE SAYING WHEN YOU'RE HEARING FRICTION, BUT THAT'S BECAUSE YOU KNOW IT'S A LOT OF WORK GOING TO THE IRB AND IT'S A LOT OF WORK WRITING AN IND. I'M NOT SURE IN THE CONTEXT

OF STEM CELL THERAPEUTICS THAT THERE'S AN EXAMPLE.

DR. HYUN: THOSE WHO WOULD ARGUE THE OTHER SIDE WOULD SIMPLY POINT THAT, WELL, THERE COULD BE THOSE REALLY DIRE CIRCUMSTANCES THAT PEOPLE WERE TALKING ABOUT, ABOUT THE EXTREMELY SERIOUS CASES FOR WHICH THE PATIENT HAS EXHAUSTED ALL ACCEPTABLE ALTERNATIVES.

DR. WAGNER: NO. BUT THEN THAT TAKES US DOWN TO THE PATH OF WHAT WE SEE OTHER COUNTRIES DOING THAT WE'VE ALL BEEN TALKING ABOUT SAYING IT MAKES US UNCOMFORTABLE, YOU KNOW, WHERE IT BECOMES THEN ALMOST A RELIGIOUS EVENT OF SAYING WE SO TRULY BELIEVE THIS IS GOING TO WORK WHEN, IN FACT, WE DON'T REALLY KNOW IT.

WHAT SURPRISES ME IS THAT THIS IS ALMOST A ROLE REVERSAL. I SHOULD BE UP THERE SAYING THIS AND YOU SHOULD BE DOWN HERE.

DR. READ: YOU'RE THE FOUNDER OR TRANSPLANTER. THEY'RE THE COWBOYS.

DR. HYUN: OKAY. OKAY. FAIR ENOUGH.

SO LET ME GO ON. IF WE'RE TALKING ABOUT A HUGE ARRAY OF POSSIBLE OPTIONS AND MANY DIFFERENT CELL TYPES AND DIFFERENT RISKS ASSOCIATED WITH THE LEVEL OF MANIPULATION AND NOVELTY OF THE CELL PRODUCT OR EXPERIENCE WITH THE CELL PRODUCT, ETC.,

THEN DOES THIS CALL ON US TO HAVE AN EXTRA SPOKE IN THE WHEEL. SO THE WHEEL IS THE IRB SYSTEM, RIGHT, FOR CLINICAL TRIALS. AND SO WHAT WE AGREED WAS THAT IT MAY NOT BE DESIRABLE TO SET UP A WHOLE OTHER REVIEW PROCESS SEPARATE FROM THE IRB ALMOST LIKE A RACK SYSTEM, RECOMBINANT DNA ADVISORY BOARD OR COMMITTEE FOR STEM CELLS.

SO WHAT WE EVENTUALLY AGREED UPON WAS THAT THERE OUGHT TO BE FOR THE IRB, OR WHAT WE CALL A HUMAN SUBJECTS REVIEW PROCESS, SUPPLEMENTAL STEM CELL-SPECIFIC EXPERTISE TO ASSESS ALL THE STEM CELL-SPECIFIC ISSUES THAT THE IRB MAY NOT BE EQUIPPED TO DO. AND, YOU KNOW, OF COURSE, THIS FOLLOWS CURRENT PRACTICE ON IRB'S TO HAVE OUTSIDE CONSULTANTS COME IN ON PROTOCOLS FOR WHICH THERE'S NO PARTICULAR STRENGTH OF EXPERTISE ON THE IRB ITSELF.

NOW, THE DOCUMENT ITSELF IS, I HAVE TO ADMIT, PEOPLE LOOK AT THE DOCUMENT AND THEY SAY, WOW, IT TOOK YOU GUYS 13 MONTHS TO DO THAT. IT'S NOT A LOT THERE. AND SO WHAT I WANT TO IMPRESS UPON YOU IS THAT ACTUALLY WE WENT THROUGH A LOT OF DISCUSSION. AND WHAT'S INTERESTING TO ME IS WHAT WE DECIDED TO LEAVE OUT.

SO THERE WAS A POINT AT WHICH THE DOCUMENT

WAS EXTREMELY LONG, AND IT WAS THIS PROCESS OF TRYING TO FIGURE OUT EXACTLY WHAT DO WE WANT THIS THING TO DO. AND WHAT WAS INTERESTING WAS WE WENT THROUGH THIS SORT OF PROCESS OF DISCOVERY OR GROWTH OF THE COMMITTEE WHERE INITIALLY PEOPLE REALLY WANTED TO DICTATE A LOT OF SPECIFICS ABOUT CULTURE CONDITIONS, ABOUT PROOF OF PRINCIPLE, ANIMAL MODELING, ALL OF THAT, AND WE REALIZED THAT'S REALLY NOT GOING TO BE VERY PRODUCTIVE, AND IT'S NOT WITHIN THE ISSCR COMMITTEE'S RESPONSIBILITY OR AUTHORITY TO DO SOMETHING LIKE THAT. WE THOUGHT THAT KIND OF FINE-GRAINED DETAIL HAS TO BE WORKED OUT THROUGH THE FDA OR THROUGH OTHER AGENCIES THAT ARE EQUIPPED TO DO THAT KIND OF THING AND HAVE THE REGULATORY AUTHORITY TO FOLLOW THROUGH.

SO WHAT WE ENDED UP WITH WERE THESE MORE GENERAL PRINCIPLES. AND, OF COURSE, GUIDELINES ARE NOT THE SAME AS REGULATIONS. GUIDELINES SET UP ASPIRATIONAL GOALS OR GENERAL PERFORMANCE STANDARDS, AND REGULATIONS ARE GOING TO BE THOSE MORE DETAILED RULES FOR WHICH THERE'S COMPLIANCE OR NONCOMPLIANCE AND THERE'S SOME WAY TO -- THERE'S SOME SANCTION AGAINST PEOPLE WHO BREAK THE REGULATIONS.

SO I'M GOING TO RETURN TO WHAT I THINK THE GUIDELINES DOCUMENT, HOW THAT RELATES TO YOUR GROUP

NEAR THE END OF MY LITTLE PRESENTATION. BUT THE CLINICAL TRANSLATION PROCESS WE KNOW HAS SEVERAL STAGES, AND SO WHAT WE DECIDED TO DO WAS TO DIVIDE OUR ENTIRE TASK FORCE OF 30 PEOPLE INTO THESE SUBCOMMITTEES TO ADDRESS EACH OF THE VARIOUS STAGES OF THE PROCESS WE HAD, SO ALL THE PROCESSING AND MANUFACTURING, PRECLINICAL STUDIES, WE HAD CLINICAL RESEARCH, AND WE HAD SOCIAL JUSTICE.

AND, OF COURSE, FOR EACH STEP OF THE PROCESS, THE MANUFACTURING, PRECLINICAL, AND CLINICAL, I DON'T WANT TO IMPLY THAT IT'S ALL GOING TO BE UNIDIRECTIONAL. OFTEN IN TRANSLATIONAL RESEARCH YOU GET CLINICAL RESEARCH THAT INFORMS MANUFACTURING OR THAT INFORMS THE PRECLINICAL STUDIES, WHERE THERE'S SORT OF A FEEDBACK LOOP BUILT IN. BUT I JUST WANT TO JUST FLAG A FEW THINGS THAT WE THOUGHT WERE STEM CELL SPECIFIC.

NOW, IN THE AREA OF MANUFACTURING, ONE OF THE KEY RECOMMENDATIONS THAT LEAPS OUT FOR ME THAT'S RELEVANT FOR OUR DISCUSSION TODAY IS THAT THERE NEEDS TO BE -- A COMMON THEME IS THERE NEEDS TO BE MORE COLLABORATION ALONG THE WAY DURING THE TRANSLATION PROCESS.

HERE'S ONE. IN THE MANUFACTURING, OUR RECOMMENDATION WAS, AMONG MANY RECOMMENDATIONS IN

THAT SECTION, WAS THAT REGULATORS AND SCIENTISTS NEED TO COLLABORATE TO COME UP WITH COMMON REFERENCE STANDARDS FOR MINIMALLY ACCEPTABLE CHANGE OF THE CELLS BECAUSE CELLS IN CULTURE WILL UNDERGO CHANGE OVER TIME. AND A LOT OF PEOPLE TALK ABOUT TOXICITY IN TERMS OF A TUMOR GROWTH POTENTIAL OR TUMORICITY, BUT SOMETIMES THEY NEGLECT THE FACT THAT CELLS IN CULTURE MAY ACCRUE MUTATIONS OR GENOMIC CHANGES THAT COULD ALSO BE HARMFUL -- PRODUCED HARMFUL EFFECTS.

SO COMMON REFERENCE STANDARDS. I MEAN THERE DOESN'T SEEM TO BE ANYTHING LIKE THAT TO KNOW EXACTLY WHAT HAVE THE REGULATORS AND THE SCIENTISTS AGREED BECAUSE REGULATORS AREN'T ALWAYS IN A POSITION TO KNOW WHAT THE SCIENTIFIC FACTS ARE AND THE SCIENTISTS ARE NOT THE REGULATORS. SO THAT'S ONE KEY RECOMMENDATION.

IN THE AREA OF PRECLINICAL STUDIES, WE NOTED THAT IT WOULD BE SHORTSIGHTED OF THE ISSCR TO SAY THAT WE HAVE TO HAVE, FOR EVERY CELL-BASED CLINICAL TRIAL TO GO FORWARD IN HUMANS, WE HAVE TO HAVE ANIMAL MODELING BECAUSE IT DEPENDS. IT DEPENDS ON THE DISEASE TO BE STUDIED AND WHETHER THERE ARE ACCEPTABLE ANIMAL MODELS FOR THAT CLINICAL CONDITION AND TISSUE PHYSIOLOGY.

SO JUST TAKE PARKINSON'S DISEASE, FOR

EXAMPLE. A LOT OF PEOPLE THINK WE NEED GOOD ANIMAL MODELS OF PARKINSON'S DISEASE. WELL, OKAY, IF YOU HAVE A RAT MODEL FOR PARKINSON'S DISEASE, YOU MAY HAVE A RAT THAT CIRCLES A CERTAIN NUMBER OF TIMES IN A TIME INTERVAL, BUT THAT'S NOT HOW PATIENTS BEHAVE WITH PARKINSON'S. THAT'S JUST A PROXY FOR SORT OF THE SYMPTOMS OF PARKINSON'S.

AND WHAT'S REALLY OF INTEREST TO PARKINSON'S DISEASE RESEARCHERS IS WHETHER OR NOT WE CAN SLOW DOWN OR STOP THE PROGRESSION OR THE DEGENERATION OF THE PATIENT'S CONDITION. SO YOU WOULD HAVE TO HAVE AN ANIMAL MODEL THAT MIMICS THAT PROGRESSION OR DEGENERATION, RIGHT. AND I'M NOT SURE IF WE CAN ACTUALLY CREATE ONE LIKE THAT.

SO WE DIDN'T WANT TO SAY YOU HAVE TO, FOR EVERY SINGLE CELL-BASED THERAPY TO GO FORWARD, HAVE TO HAVE ANIMAL MODELS BECAUSE IT DEPENDS. IT DEPENDS. AND DO YOU HAVE TO HAVE A LARGE ANIMAL MODEL? AGAIN, IT DEPENDS. SO YOU SEE THAT GIVEN THE ENORMOUS ARRAY OF POSSIBLE INTERVENTIONS, YOU REALLY HAVE TO TAKE IT ON A CASE-BY-CASE BASIS. SO THE FRAMEWORK HAS TO BE SUCH THAT IT'S FLEXIBLE TO DEVELOPMENTS IN THE FIELD, IT'S FLEXIBLE TO A PARTICULAR DISEASE THAT INVESTIGATORS WANT TO STUDY AND THEIR APPROACH.

WHEN YOU ARE PERFORMING CELL CULTURES IN ANIMAL STUDIES IN PRECLINICAL RESEARCH, OUR OTHER RECOMMENDATION IS THAT THESE CELL CULTURES IN ANIMAL STUDIES SHOULD BE USED TO TEST INTERACTION WITH DRUGS THAT THE RECIPIENT IS EXPECTED TO TAKE. DRUG INTERACTION IS ANOTHER MAJOR RECOMMENDATION.

NOW, WHEN WE GET TO THE CLINICAL SIDE, CLINICAL RESEARCH SIDE, I'M NOT GOING TO REPEAT MUCH OF THE STUFF THAT I'VE HEARD THIS MORNING BECAUSE I THINK THE PRESENTERS DID A VERY GOOD JOB SORT OF LAYING OUT WHAT SOME OF THE KEY ISSUES ARE THERE. BUT A FEW THINGS THAT I WANT TO FLAG THAT MAY BE RELEVANT FOR YOUR THINKING ABOUT HOW YOU MIGHT WANT TO SET UP THE REQUIREMENTS FOR INFORMED CONSENT FOR CLINICAL RESEARCH.

ONE IS WHO GETS TO CONDUCT THE INFORMED CONSENT INTERVIEW? JUST TO TAKE SOME OF THE SUGGESTIONS LIKE APPLEBAUM, WHICH IS ONE OF THE AUTHORS NOTED BY PREVIOUS PRESENTERS. APPLEBAUM EVEN GOES SO FAR AS TO SUGGEST THAT THE PERSON WHO CONDUCTS THE INFORMED CONSENT INTERVIEW NOT BE A MEMBER OF THE RESEARCH TEAM, MIGHT EVEN WEAR A DIFFERENT COAT, A RED COAT OR ORANGE COAT, SOMETHING TO SAY, LOOK, I'M DIFFERENT AND I REPRESENT -- I DON'T REPRESENT ANY OF THE INTERESTS OF RESEARCH

TEAM.

SOMETHING THAT HASN'T REALLY BEEN EXPLORED VERY MUCH IS THE FACT THAT SOME OF THESE CLINICAL TRIALS MAY OCCUR IN PEOPLE WHO DON'T HAVE THE CAPACITY TO CONSENT, THE CHILDREN OR INCAPACITATED OLDER ADULTS. SO I THINK YOU HAVE TO THINK VERY CAREFULLY ABOUT WHAT REQUIREMENTS WE SHOULD HAVE FOR SURROGATES SO MAKE THESE DECISIONS ON BEHALF OF OTHERS WHO WILL UNDERGO THE EXPERIMENT.

WHAT WAS EMPHASIZED AGAIN AND AGAIN BY THE MEMBERS OF OUR COMMITTEE WAS THAT THERE HAS TO BE A CLEAR AND TIMELY AND EFFECTIVE PLAN FOR ADVERSE EVENT REPORTING AND SOME CLINICAL PLAN IN PLACE TO PROVIDE TREATMENT FOR ADVERSE EVENTS.

IN LISTENING TO SOME OF THE DEBATE THAT WAS HAPPENING BACK AND FORTH THIS MORNING ABOUT WHETHER OR NOT INVESTIGATORS ARE REALLY GOING TO HAVE THE RIGHT MOTIVATION TO DO THIS, A THOUGHT OCCURRED IN MY MIND OF I'M SKEPTICAL OF EVEN TRYING TO PUT THE ONUS ON THE INVESTIGATOR TO BE FORTHCOMING WITH THIS DATA. I THINK IF YOU HAVE AN ACCESS PLAN IN PLACE THAT YOU REQUIRE, AND IF PEOPLE ACTUALLY ARE HARMED, THEY'RE GOING TO BE TREATED, RIGHT. AND SO THERE COULD BE A WAY IN WHICH THE REPORTING HAPPENS FROM NOT THE INVESTIGATOR

SELF-REPORTING, BUT THROUGH THIS SORT OF MONITORING SYSTEM OF CARE PROVIDERS OR OTHER PEOPLE WHO ARE BETTER SET UP TO LOOK AFTER THE PATIENT'S PERSONAL INTEREST AND NOT THE RESEARCH TEAM WHICH DOESN'T NECESSARILY HAVE THE PATIENT'S PERSONAL INTEREST FOREMOST IN MIND.

NOW, A MAJOR ISSUE THAT NOBODY REALLY COULD COME UP WITH A CLEAR RECOMMENDATION ON WAS HOW LONG DO YOU MONITOR THE PATIENTS OR THE PARTICIPANTS OF THE RESEARCH. AND WHAT COUNTS AS AN ADVERSE EVENT. HOW WOULD YOU KNOW THAT THAT'S RELATED TO THE STEM CELL-BASED INTERVENTION? SO A LOT OF PEOPLE WHO UNDERGO -- WHO WOULD UNDERGO THESE TRIALS ARE SERIOUSLY ILL, AND THEY ARE LIKELY TO GET WORSE AND WORSE. SO HOW COULD YOU EXACTLY ATTRIBUTE THE SO-CALLED LATER ADVERSE EVENT OR DETERIORATION TO SPECIFICALLY THE CELL-BASED THERAPY? THAT MIGHT BE A GOOD ARGUMENT FOR HAVING THE SHAM GROUP.

I'M GOING TO SKIP OVER SOME OF THE THINGS I HAD PLANNED BECAUSE I WANT TO GET ON TO DISCUSSION. BUT YOU WILL NOTICE THAT ONE OF THE FOUR MAJOR SECTIONS OF THE GUIDELINES DOCUMENT HAD TO DO WITH SOCIAL JUSTICE. AND I HAVE TO SAY OF THE INTERNATIONAL GROUP, THIS SECTION RESONATED QUITE DEEPLY WITH THE MEMBERS OF THE COMMITTEE WHO WERE

FROM EUROPE WHERE I THINK SOLIDARITY AND SOCIAL JUSTICE IS KIND OF A LITTLE BIT MORE FOREFRONT IN THEIR NATIONAL CONSCIOUSNESS.

AND DURING THE PUBLIC REVIEW PROCESS, PUBLIC COMMENT PROCESS, THE COMMENTATORS FROM EUROPE WERE ESPECIALLY HAPPY THAT WE HAD THAT SECTION IN THERE. AND I THINK IT'S KIND OF AN INTERESTING COMMENT ON CULTURES, BUT THE MOST PUSHBACK WE GOT WERE FROM THE AMERICANS. SURPRISE.

SO I JUST WANTED TO POINT OUT ONE THING ABOUT THE SOCIAL JUSTICE SECTION, AND THAT WAS I THINK A KEY RECOMMENDATION WE HAD THERE AND ONE THAT YOU MIGHT TRY TO TAKE TO HEART IN YOUR OWN APPROACH IS THAT WE REALLY ENCOURAGED THE DEVELOPMENT AND THE ASSESSMENT OF ALTERNATIVE MODELS OF INTELLECTUAL PROPERTY, LICENSING, PRODUCT DEVELOPMENT, AND PUBLIC FUNDING TO PROMOTE FAIR AND BROAD ACCESS TO STEM CELL-BASED THERAPIES. I THINK THAT CIRM IS IN THE UNIQUE POSITION TO COME UP WITH SOME OF THOSE CREATIVE METHODS, AND I WOULD ENCOURAGE YOU TO DO THAT.

SO IN SUMMARY, THE GUIDELINES ARE SUPPOSED TO REPRESENT A BASIC FOUNDATION OF AGREED UPON CONSENSUS PRINCIPLES AT LEAST AMONG THOSE REPRESENTING THE ISSCR AND THOSE WHO PARTICIPATED IN

THE PUBLIC COMMENT PROCESS.

NOW, IT'S UP TO PEOPLE LIKE YOU TO COME UP WITH -- TO BRING THOSE GUIDELINES DOWN TO EARTH AND TO COME UP WITH REGULATIONS AT THE LOCAL LEVEL, ENFORCEABLE ONES. WE HAVE THE FOUNDATION. NOW YOU GOT TO BUILD THE HOUSE. YOU GOT TO BUILD A HOUSE THAT'S GOING TO BE SPECIFIC TO SORT OF THE INSTITUTIONAL CLIMATE THAT YOU FIND YOURSELVES IN HERE.

ONE WAY TO -- MY FURTHER RECOMMENDATION IS, GIVEN THE ENORMOUS ARRAY OF POSSIBLE INTERVENTIONS AND APPROACHES AND CELLS TO BE USED AND WHAT'S DONE TO THE CELLS, AT THE MORE LOCAL LOCAL LEVEL AS YOU GO FURTHER FURTHER DOWN FROM HEAVEN AND CLOSER TO EARTH, I'VE HEARD ABOUT THESE DISEASE GROUPS THAT YOU'RE THINKING ABOUT. I THINK THAT'S AN EXCELLENT WAY TO GO IN TERMS OF COLLABORATIONS THAT NEED TO BE IN PLACE AND WHAT NEEDS TO BE THOUGHT THROUGH IN TERMS OF ANIMAL MODELING SPECIFIC TO THAT DISEASE STATE.

SO I THINK THAT YOU, YOU, CIRM, ARE IN A VERY INTERESTING POSITION BECAUSE I'VE HEARD ALSO TODAY SORT OF A LOT OF COMMENT ON HOW VARIOUS ACTORS BEHAVE IN THE CURRENT SITUATION, HOW BIOTECH TENDS TO BEHAVE IN PROTECTING THEIR INTELLECTUAL PROPERTY,

ETC. BUT IN SOME WAYS I DON'T KNOW IF THIS IS JUST BECAUSE I'M KIND OF COMING IN FROM THE OUTSIDE AND LOOKING AT WHAT YOU'RE DOING, BUT YOU HAVE TO REALIZE YOU'RE THOUGHT LEADERS IN THIS AREA. AND IT'S SORT OF UP TO YOU TO SHAPE THE ENVIRONMENT THAT WILL CHANGE HOW SOME OF THESE ACTORS BEHAVE.

SO I THINK I DIDN'T GET THE IMPRESSION THAT YOU REALLY APPRECIATED ENOUGH THE INFLUENCE YOU'RE ACTUALLY GOING TO HAVE, NOT JUST IN CALIFORNIA, BUT I'M TALKING ABOUT INTERNATIONALLY BECAUSE PEOPLE WILL LOOK TO WHAT CALIFORNIA HAS DONE AND THAT WILL BE A PRECEDENT.

SO I CONGRATULATE YOU IN THINKING PROACTIVELY ABOUT THESE ISSUES, BUT I THINK YOU NEED TO ALSO BE AWARE THAT YOU'RE IN A POSITION OF TREMENDOUS INFLUENCE AND THAT YOU TAKE THAT RESPONSIBILITY TO HEART. OKAY. SO I THINK I WANT TO JUST STOP THERE AND JUST CONTINUE ON WITH THE DISCUSSION.

CHAIRMAN LO: THANKS VERY MUCH. WHY DON'T YOU STAY BECAUSE I THINK WE'RE GOING TO HAVE QUESTIONS DIRECTED TO YOU. ALTA, I KNOW YOU HAD ONE. WHY DON'T YOU GO FIRST.

DR. CHARO: THANKS VERY MUCH, INSU. I WANTED TO RETURN YOU TO SOMETHING YOU TALKED ABOUT

TOWARD THE BEGINNING AND WHERE, IN FACT, JOHN HAD PICKED UP ON IT ABOUT THE PHENOMENON OF MEDICAL INNOVATION OUTSIDE OF A CLINICAL TRIAL. AND IT'S A TRICKY BUSINESS HERE BECAUSE, OF COURSE, TO THE EXTENT YOU ARE WORKING WITH MANIPULATED TISSUES IN A WAY THAT TRIGGERS FDA OVERSIGHT, YOU'RE FORCED INTO CLINICAL TRIALS.

BUT WHEREVER THERE IS SOME LOOPHOLE, SOME OPENING FOR MEDICAL INNOVATION, I WAS WONDERING HAS ANYBODY STARTED TO THINK ABOUT THE INTERPLAY BETWEEN THAT AND THE UPCOMING EMPHASIS ON COMPARATIVE EFFECTIVENESS RESEARCH? BECAUSE IN A SENSE THAT RESEARCH, WHICH IS GOING TO BE EVIDENCE-BASED MEDICINE, IS EITHER SOMETHING THAT YOU COULD THINK OF AS THREATENING ALL THIS MEDICAL INNOVATION BECAUSE IT'S GOING TO BE SCARY TO DO THESE THINGS AND THEN BE FOUND OUT LATER. OR YOU COULD THINK OF IT IN THE ALTERNATIVE AS A SAFETY NET SO THAT YOU CAN GO AHEAD AND INNOVATE MORE QUICKLY KNOWING THAT EVENTUALLY THERE'S GOING TO BE A RETROSPECTIVE LOOK. BUT I'M JUST WONDERING IF ANYBODY HAS STARTED TO EVEN THINK ABOUT THIS.

DR. HYUN: NOT TO MY KNOWLEDGE.

DR. CHARO: THERE'S GOING TO BE A TON OF MONEY ON COMPARATIVE EFFECTIVENESS COMING OUT OF THE

FEDERAL GOVERNMENT FROM THE STIMULUS PACKAGE.

DR. HYUN: OH, BOY. I'M NOT AWARE OF ANYBODY.

DR. CHARO: I JUST RAISE IT FOR THE RECORD BECAUSE IT'S SOMETHING WE MIGHT WANT TO THINK ABOUT TAKING ADVANTAGE OF. THAT MONEY IS GOING TO BE FLOWING TO THE STATES AND TO THE INSTITUTIONS; AND IF THERE ARE INNOVATIONS THAT HAVE TAKEN PLACE BEFORE WE HAD OPTIMAL PROTECTIONS IN PLACE OR OPTIMAL THINKING ABOUT HOW TO STRUCTURE TRIALS OR BEFORE THE FDA HAD GOTTEN THOROUGHLY AGGRESSIVE ABOUT ITS REGULATION HERE, I MEAN THIS IS SOMETHING WE MIGHT THINK ABOUT TRYING TO IDENTIFY IF THERE'S A NEED FOR IT IN ANY SPECIFIC AREAS THAT RELATE TO OUR WORK AND BE ABLE TO PROPOSE RESEARCH THAT COULD BE FUNDED FOR THAT.

CHAIRMAN LO: OTHER COMMENTS, QUESTIONS FOR INSU? ROB TAYLOR.

DR. TAYLOR: YEAH, INSU, I WANTED TO ACTUALLY FOLLOWING UP A LITTLE BIT ON ALTA'S COMMENTS. I'M NOT SO SURE WHAT'S GOING TO HAPPEN UNDER THE MEDICAL INNOVATION MODEL. IT'S A LITTLE BIT HAZIER; BUT UNDER THE SORT OF MORE TRADITIONAL CLINICAL TRIALS MODEL, ADVERSE EVENTS, I THINK, WILL BE REPORTED THROUGH DSMB'S. I THINK THERE ARE

DEFINITELY -- FOR THESE TYPES OF PROTOCOLS, I CAN'T IMAGINE THAT THEY'LL GO THROUGH AN IRB WITHOUT AN ASSIGNED DATA SAFETY MONITORING BOARD IN ADDITION TO SORT OF A PLAN.

SO I WOULD SAY THAT IN THAT SETTING I'M NOT REALLY PARTICULARLY CONCERNED ABOUT INVESTIGATORS SORT OF SUBMITTING ADVERSE EVENTS.

IN THE MEDICAL INNOVATION MODEL, THAT'S A LITTLE BIT MORE OF A CONCERN AND MAYBE WOULD REQUIRE, IF YOU'RE GOING TO GO IN THAT DIRECTION, AND THAT'S KIND OF AN INTERESTING THOUGHT AND I KIND OF RAISED THE SORT OF GENERAL QUESTION YESTERDAY WHEN DOBKIN PRESENTED HIS STUFF, AS TO WHETHER THERE MIGHT BE A DIFFERENT MODEL OTHER THAN SORT OF A CLINICAL TRIAL. AND THIS DIDN'T REALLY GET EXPANDED UPON, BUT YOU'VE SORT OF RAISED IT AGAIN NOW. AND I WOULD THINK WE'D NEED SOME GOOD TYPE OF ADVERSE EVENT REPORT.

DR. HYUN: MY REASON FOR BRINGING THAT ISSUE UP WAS, AND I PROBABLY DIDN'T EXPRESS IT VERY CLEARLY MY MOTIVATION FOR BRINGING THAT UP. I PROBABLY DIDN'T EXPRESS IT VERY CLEARLY. I'M NOT MAKING UP HERE ANY KIND OF -- THIS IS WHY I DON'T THINK WE NEED TO SWITCH PLACES, JOHN. I'M NOT MAKING ANY SORT OF NORMATIVE PLAN THAT WE OUGHT TO

GO THAT WAY, BUT IT'S MORE OF ALMOST A FATALISTIC KIND OF ATTITUDE LIKE IT'S GOING TO HAPPEN. PEOPLE ARE GOING TO DO IT. CIRM CAN'T PREVENT PEOPLE FROM TRYING THAT OR FUNDERS CAN'T PREVENT.

SO IF IT'S GOING TO HAPPEN, AS SOON AS YOU SAY SOMETHING, SOMETHING ABOUT HOW YOU THINK IT SHOULD HAPPEN, IF IT'S GOING TO HAPPEN AT ALL, SOME PEOPLE DON'T LIKE THAT ATTITUDE. THEY KIND OF FEEL LIKE SAYING, WELL, THAT'S JUST AS GOOD AS ENDORSING IT. I DON'T THINK THAT'S NECESSARILY TRUE. BUT I THINK IT'S SOMETHING TO KIND OF THINK ABOUT BECAUSE EVERYTHING THAT YOU HEAR ABOUT IN THE NEWS OR EVEN THE PAPER THAT WAS PUBLISHED ON TUESDAY, IT'S ALWAYS IN THAT CONTEXT OF SOMEBODY SAYING I'M GOING TO PROVIDE YOU WITH CARE BECAUSE THERE'S NOTHING ELSE THAT'S WORKING FOR YOU. COME SEE ME. AND IT'S NOT RESEARCH AND IT'S PRESENTED IN A VERY DIFFERENT WAY. IT'S IN A DIFFERENT SORT OF CULTURE, YOU KNOW, OF PRACTICE OR HOW THE INTERVENTION IS BEING PRESENTED AND THOUGHT ABOUT.

SO I THINK YOU HAVE TO PAY ATTENTION TO THAT, AND I DON'T KNOW HOW YOU'RE GOING TO ACTUALLY ADDRESS THAT, BUT I THINK THAT'S WHY WE COULD NOT BE SILENT ON THAT IN THE ISSCR DOCUMENT. I THINK IT WOULD HAVE BEEN EVEN WORSE NOT TO SAY ANYTHING

BECAUSE, WHAT, ALL THE STEM CELL CLINICS ARE USING THAT SORT OF PHRASING, INNOVATIVE, YOU KNOW, RESEARCH HAS BEEN SLOWED DOWN IN THE U.S., COME HERE WHERE WE'RE UNFETTERED AND WE HAVE THE LATEST FOR YOU, PRAYING ON PATIENT'S HOPES ETC. SO WE COULDN'T BE SILENT ON THAT.

IF WE'RE GOING TO SAY SOMETHING, WHAT ARE YOU GOING TO SAY? SO I WANTED TO JUST BE A LITTLE BIT CLEAR. I'M NOT, LIKE, SAYING THAT I'M ENDORSING THEM; BUT I THINK ANY TIME YOU HAVE A DIALOGUE ABOUT CLINICAL TRIALS OR TRANSLATIONAL RESEARCH IN SOME REALLY FRONTIER AREA LIKE THIS WITH EXPECTATIONS, I THINK IT WOULD BE WRONG TO IGNORE THAT PART OF THE CONVERSATION.

SO I DON'T REALLY KNOW WHAT MY RECOMMENDATION TO YOU WOULD BE IN TERMS OF POLICY, BUT I THINK YOU HAVE TO ADDRESS IT BECAUSE PEOPLE ARE GOING TO COME BACK AND SAY -- I'VE ACTUALLY REVIEWED PROPOSALS ALONG THE LINES OF, WELL, I THINK IT SHOULD ALWAYS -- THAT STEM CELL-BASED THERAPIES OR APPROACHES OR INTERVENTION SHOULD ONLY BE AVAILABLE IN THE CONTEXT OF A CLINICAL TRIAL.

I THINK WHAT'S GOING TO HAPPEN IS ALL THESE STEM CELL CLINICS ARE GOING TO SAY BE IN OUR CLINICAL TRIAL. THEY'RE GOING TO JUST REPHRASE IT.

IT'S NOT GOING TO GET RID OF THE PROBLEM. SO YOU HAVE TO SORT OF CONFRONT IT AT SOME POINT. I DON'T KNOW -- I SORT OF IDENTIFIED THE PROBLEM. I DON'T HAVE A NORMATIVE SOLUTION EXCEPT TO SAY I THINK YOU HAVE TO SAY SOMETHING.

CHAIRMAN LO: LET ME ADD SOME THINGS HERE FOR JOHN AND ROD AND SORT OF CONTEXT. I WAS A MEMBER OF INSU'S COMMITTEE AND SORT OF WAS PART OF THESE DISCUSSIONS. AND JUST TO SORT OF GIVE A BACKGROUND AND CONTEXT, A STARTING POINT WAS A SENSE THAT STEM CELLS ARE BEING USED FOR THERAPY IN OTHER COUNTRIES WITHOUT ANY ATTEMPT TO ASSESS OUTCOMES. BRUCE DOBKIN TALKED ABOUT THAT A LITTLE BIT. THERE'S BEEN A COUPLE PAPERS IN *PLOS* MEDICINE ON THIS.

SO WE STARTED OUT WITH A STRONG SENSE THAT THAT WAS TO BE VERY MUCH DISCOURAGED. THEN YOU HAD OTHER PEOPLE SAYING, BUT WAIT A MINUTE. IF YOU TAKE THE EXTREME POSITION THAT EVERYTHING HAS TO GO, EVERY STEM CELL INNOVATION TO BE IN A CLINICAL TRIAL, YOU ARE SHUTTING OUT THINGS THAT ARE DONE, WHICH ARE, I GUESS, JOHN, CORRECT ME IF I GET THE EXAMPLES WRONG, BUT SORT OF MODIFICATIONS OF CURRENT ACCEPTED THERAPIES. SO IF YOU'RE DOING AUTOLOGOUS STEM CELL TRANSPLANTATION, BONE MARROW

TRANSPLANTATION OR OTHERS, AND YOU'RE MAKING SMALL MODIFICATIONS IN THE RETRIEVAL PROCESS, OR YOU'RE SLIGHTLY ENLARGING THE SCOPE OF PERSONS YOU'RE DOING THE INTERVENTION IN, OFTEN PEOPLE WILL DO THOSE EXTENSIONS NOT WITH A FORMAL CLINICAL TRIAL, BUT TRYING IT IN ONE OR TWO PATIENTS.

THE ISSCR DOCUMENT SAID THERE'S A LIMIT ON THE NUMBER OF CASES YOU CAN DO AS THAT SORT OF INNOVATION. ONCE YOU BEGIN TO SAY, WELL, THIS LOOKS LIKE IT MAY REALLY WORK, THE THOUGHT WAS YOU SHOULD THEN PROCEED TO A CLINICAL TRIAL. WE ALSO -- THE ISSCR ALSO SAID THE CONSENT PROCESS SHOULD MAKE IT CLEAR THIS IS INNOVATIVE, UNPROVEN THERAPY, AND THERE'S AN OBLIGATION TO SORT OF ASSESS THE OUTCOME. SO THAT WAS SORT OF THE DYNAMIC BACK AND FORTH.

DR. WAGNER: AGAIN, I CANNOT POSSIBLY UNDERSTAND THIS CONVERSATION WITHOUT HAVING A REAL -- I NEED TO HEAR A REAL EXAMPLE OF SOMETHING. EVEN CHANGING -- WHAT IS THE PURPOSE OF DESIGNING A CLINICAL TRIAL? IT'S MORE THAN JUST BEING ABLE TO PUBLISH IT. IT'S MORE THAN COMMUNICATING TO THE COMMUNITY WHAT YOU'RE DOING. IT'S ALSO A WAY OF TRYING TO AT LEAST IDENTIFY, IF NOT CONTROL, THE VARIABLES IN TERMS OF BEING ABLE -- AT THE END OF THE DAY BEING ABLE TO ASSESS IS THIS DOING

SOMETHING? HOW CAN YOU POSSIBLY SAY A FEW PATIENTS AND THEN POSSIBLY DECIDE THAT THAT'S DOING SOMETHING BENEFICIAL WHEN YOU'VE DONE NOTHING UP FRONT TO TRY TO CONTROL SOME OF THOSE VARIABLES OR AGAIN AT LEAST IDENTIFY WHAT THE VARIABLES MIGHT BE IN ADVANCE?

NOW, AGAIN, THERE MAY BE EXAMPLES THAT I CANNOT YET THINK OF. I THINK IT IS TRUE THAT THERE ARE INSTITUTIONS IN THE UNITED STATES THAT DO THIS TYPE OF WORK, AND MAYBE IT DOES LEAD TO SOMETHING BIGGER IN A MORE FORMAL WAY. I'M NOT -- I DON'T BELIEVE IT'S THE RIGHT THING TO DO. AND AGAIN, I CAN'T THINK OF A SINGLE EXCEPTION, BUT THERE MIGHT BE. I JUST CAN'T THINK OF WHAT THEY WOULD BE.

DR. HYUN: BY THE WAY, THE OVERALL TONE OF THE RECOMMENDATIONS IS WE ALWAYS WANTED TO LEAVE ASSESSMENT DOORS OPEN AS POSSIBLE WITHOUT CAUSING HARM. SO PEOPLE -- WHAT YOU SAID, I GUESS I'M NOT SURE EXACTLY WHAT THE EXAMPLE WOULD BE.

DR. WAGNER: BUT PURELY SCIENTIFIC POINT OF VIEW. YOU KNOW, THEN THE BEST YOU'RE HOPING FOR IS ANECDOTAL INFORMATION THAT REALLY -- AGAIN, AS MARIE SAID EARLIER, WE WANT TO COLLECT SOME OF THAT INFORMATION BECAUSE THAT MIGHT PROVIDE US WITH SOME CLUES, BUT THAT'S NOT REALLY THE WAY OF DOING SCIENCE. I MEAN THAT'S NOT REALLY THE WAY

ESPECIALLY WHEN WE'RE TALKING ABOUT A THERAPY THAT WE SPENT THE FIRST DAY AND A HALF OF THIS MEETING TALKING ABOUT THIS IS A RISKY BUSINESS.

NOW, IN THE CONTEXT OF BONE MARROW TRANSPLANT, REMEMBER THAT 20 PERCENT OF THE PATIENTS WILL DIE BEFORE DAY 100 AFTER THE THERAPY. AND, YES, THIS IS THE STANDARD OF CARE IN MANY PARTICULAR DISEASES. WE'VE ACCEPTED THAT, BUT THAT'S ALSO IN THE CONTEXT OF, YOU KNOW, A SPECIFIC TYPE OF PATIENT POPULATION THAT NOT ONLY HAS NO OTHER ALTERNATIVE THAT'S CONSIDERED TO BE AS GOOD BECAUSE AT LEAST THERE'S A KNOWN CURATIVE INTENT, BUT AT THE SAME TIME WE MIGHT TWEAK THE SYSTEM LIKE YOU WERE SUGGESTING. THERE COULD BE SOMETHING, BUT NOT KNOWING EXACTLY WHAT YOU'RE THINKING, EVEN THAT NEEDS TO BE REREVIEWED SO THAT YOU CAN ASSESS WHETHER OR NOT THAT TWEAK THAT YOU DID HAS SOME IMPACT.

BUT MOST IMPORTANT -- I THINK WHAT MAKES BONE MARROW TRANSPLANT IN PARTICULAR A CHALLENGE IS THAT OFTENTIMES THE ACCEPTED PART OF THE THERAPY IS ACTUALLY THE RISKIEST PART OF THE THERAPY. AND THAT THE TWEAKING YOU'VE DONE, WHICH IS THE CLINICAL TRIAL, MAY HAVE ITS OWN RISK, BUT IT PALES BY COMPARISON OF THE UNDERLYING THERAPY FOR WHICH IS

THE STANDARD OF CARE. BUT THAT'S A UNIQUE TWIST TO ALL THIS. IN ANY CASE, I'M JUST RAMBLING AT THIS POINT. BUT AGAIN, I DON'T KNOW THAT I CAN IDENTIFY A SINGLE CIRCUMSTANCE, AND I DON'T KNOW THAT WE SHOULD EVEN CONSIDER THE POSSIBILITY OF CIRM FUNDING OR ANYBODY'S FUNDING FOR SOMETHING UNLESS WE COME UP WITH SOME CONCRETE EXAMPLE AND MAYBE PUT OUR ARMS AROUND WHAT THIS MIGHT BE.

CHAIRMAN LO: JEFF.

MR. SHEEHY: THIS IS -- FIRST, I'M NOT EVEN SURE I REALLY UNDERSTAND THIS AT THIS POINT. I WONDER IF THIS IS AN ISSUE THAT WE MIGHT SET UP AND ACTUALLY, IF WE ARE INDEED THOUGHT LEADERS, BECAUSE IT IS IN THIS DOCUMENT -- I'VE GOT THE DOCUMENT UP IN FRONT OF ME -- THAT PERHAPS WE SHOULD TAKE A FORMAL POSITION ON OR THINK ABOUT A LITTLE MORE DEEPLY BECAUSE GIVEN THE UNIQUE NATURE OF CIRM AND THE INCREDIBLE SUPPORT FROM THE PATIENT ADVOCACY COMMUNITY, YOU CAN SEE THIS BEING VERY PROBLEMATIC AT SOME POINT DOWN THE ROAD IF YOU DO HAVE THIS IDEA OF MEDICAL INNOVATION AND PEOPLE DOING THIS IN PLACES WHERE THERE AREN'T THE SAME STANDARDS OF CLINICAL TRIAL MENTALITY. AND IT MIGHT BE BETTER FOR US TO ADDRESS THIS BEFORE WE HAVE THE CURE IN CHINA OR THE CURE IN RUSSIA TO REALLY KIND OF DEFINE

THE ISSUE. BECAUSE I DON'T THINK -- THIS HAS JUST KIND OF BEEN THROWN OUT HERE. WE DON'T HAVE ALL THAT WE NEED TO KNOW AND IT'S VERY PROVOCATIVE. AND I WOULD LIKE TO KIND OF GET TO THE BOTTOM OF IT.

I AM KIND OF SURPRISED BECAUSE IT DOES SEEM THOUGH -- MY BEST FRIEND HAD A BABOON MARROW TRANSPLANT, SO WACKY STUFF DOESN'T NECESSARILY FREAK ME OUT. I THINK WE MIGHT --

CHAIRMAN LO: STEVE PECKMAN.

DR. PECKMAN: I'M NOT SURE I ACTUALLY UNDERSTAND THE CONCEPT OF MEDICAL INNOVATION EITHER EXCEPT I KNOW IT EXISTS IN THINGS LIKE SURGERY WHERE SURGERIES ARE MODIFIED IN THE MIDDLE OF A PROCEDURE, AND YOU COME UP WITH AN INNOVATIVE TECHNIQUE. NEVERTHELESS, I THINK THAT THE ISSCR DOCUMENT EXISTS IN A CONTEXT THAT CIRM DOES NOT, WHICH IS IT EXISTS IN AN INTERNATIONAL CONTEXT WHICH IS TRYING TO ADDRESS A BROAD INTERNATIONAL AUDIENCE. CIRM BEING A PART OF THE STATE OF CALIFORNIA, BEING PART OF THE UNITED STATES OF AMERICA IS SUBJECT TO THE RULES AND LAWS OF THE COUNTRY, WHICH INCLUDE FDA REGULATION ABOUT USE OF CELLULAR ARTICLES IN TERMS OF IND'S AND ETHICS REVIEWS AND EVERYTHING ELSE.

AND SO DEPENDING ON THE TYPE OF INNOVATION THAT WE'RE TALKING ABOUT, AND JOHN AND INSU HAVE

REALLY ARTICULATED SOME DIFFERENCES THERE, IT MAY NOT BE POSSIBLE TO ENGAGE IN A LARGE MULTITUDE OF INNOVATIONS THAT ONE MIGHT WANT TO THAT MAY BE OCCURRING IN OTHER COUNTRIES. AND SO THERE ARE ALREADY RESTRICTIONS THAT WE WORK WITHIN THAT ARE GOING TO ADDRESS A LOT OF THESE ISSUES.

NEVERTHELESS, JEFF, I THINK THAT ONE OF THE THINGS WE DO HAVE TO UNDERSTAND WITHIN THE ISSCR CONTEXT IS THE CURES ALREADY EXIST IN RUSSIA AND CHINA, AND THEY'RE BEING ADVERTISED AS EXISTING, AND WE NEED TO BE AWARE OF THAT AND INCLUDE THAT IN OUR THINKING. BUT IT MAY NOT BE NECESSARILY SOMETHING THAT CIRM NEEDS TO BE CONCERNED ABOUT IN CRAFTING GUIDELINES FOR RESEARCH THAT YOU'RE GOING TO FUND.

DR. HYUN: HERE'S HOW IT MIGHT INTERSECT. SO YOU'RE ABSOLUTELY RIGHT. YOU HAVE A VERY LARGE DISEASE -- PATIENT ADVOCACY THRUST TO EVERYTHING THAT CROSSES YOUR MIND. WHAT I'M CONCERNED ABOUT IS THAT YOU'LL GET PEOPLE WHO SAY, WELL, NOW IF YOU SAY EVERYTHING SHOULD BE IN THE CLINICAL TRIAL, THEN WHAT ABOUT COMPASSIONATE USE? YOU WILL GET A LOT OF PUSH IN THAT DIRECTION. SO I THINK YOU HAVE TO BE PREPARED TO HAVE SOME STANCE ON WHAT YOU THINK WOULD BE ACCEPTABLE.

IF SOMEONE SAYS, WELL, WHY AREN'T YOU

FUNDING MEDICAL INNOVATIONS AND WHY AREN'T YOU FUNDING THESE OTHER THINGS, YOU HAVE TO HAVE --

CHAIRMAN LO: LET ME ASK ALTA TO STEP IN HERE FOR A MINUTE BECAUSE THE REGULATORY SORT OF ANSWER TO THIS IS JUST PRETTY CLEAR-CUT RIGHT NOW.

DR. READ: I WAS GOING TO SAY WE'RE A COUNTRY OF LAWS, AND YOU KIND OF HAVE TO FOLLOW THE LAW. THERE ARE LAWS. SO I MEAN I THINK THAT'S THE BOTTOM LINE.

I WAS JUST GOING TO GIVE AN EXAMPLE OF A MEDICAL INNOVATION THAT WAS OCCURRING, AND SOME OF US FOUND OUT ABOUT IT AND HAD A CONFERENCE CALL, AND THE FDA PERSON FOUND OUT ABOUT IT AND THEY GOT THEIR LETTER AND GOT SHUT DOWN A FEW MONTHS LATER. IT WAS A PHYSICIAN IN COLORADO WHO WAS TAKING CELLS OR CARTILAGE OUT OF PEOPLE'S KNEES AND IT WAS AUTOLOGOUS, AND HE SAID, WELL, IT'S NOT INTERSTATE AND IT'S AUTOLOGOUS. BUT WHAT HE WAS DOING IS HE WAS TAKING THE TISSUE BACK TO THE LAB AND CULTURING IT AND THEN CREATING A PRODUCT TO PUT BACK IN THESE PEOPLE'S KNEES.

AND YOU MIGHT SAY, WELL, WHAT'S WRONG WITH THAT? WELL, WHAT'S WRONG WITH THAT IS THAT IT'S MORE THAN MINIMALLY MANIPULATED. AND SO IT FITS THE DEFINITION OF A 351 HCTP, AND YOU NEED AN IND, AND

THEN YOU HAVE TO GET A BIOLOGICS LICENSE APPLICATION.

SO IT DOESN'T MATTER IF IT'S NOT INTERSTATE TRANSPORT. HE WAS BREAKING THE LAW. AND SO ACTUALLY THE FDA IS GETTING AFTER HIM NOW, AND I THINK -- I DON'T KNOW IF THE COMPANY IS SHUT DOWN YET, BUT IT'S A PROBLEM. YOU JUST CAN'T DO THAT.

DR. CHARO: I THINK IT'S REALLY IMPORTANT TO RECOGNIZE THAT THE FDA'S ACTIONS IN THIS AREA HAVE BEEN EVOLVING OVER THE LAST 15 YEARS. MANY OF THE STORIES AND MANY OF THE PRACTICES THAT WE TALK ABOUT ARE THINGS THAT COME FROM A DECADE OR A DECADE AND A HALF AGO BEFORE THEY HAD THEIR TISSUE ACCESS PLAN AND BEFORE THEY MORE AGGRESSIVELY STARTED INSISTING ON THE USE OF IND'S BEFORE YOU BEGIN DOING HUMAN CELL THERAPIES IN ANY CONTEXT.

AND BECAUSE IN MANY WAYS WE HAVE A SELF-REPORT SYSTEM IN THE U.S.; THAT IS, I AS A SURGEON, FOR EXAMPLE, HAVE TO RECOGNIZE THAT WHAT I'M DOING IS A REGULATED ACTIVITY AND PRESENT MYSELF TO THE FDA. IT'S ENTIRELY POSSIBLE THERE ARE LOTS OF SURGEONS STILL DOING THINGS THAT, IN FACT, SHOULD HAVE GOTTEN AN IND, BUT IT NEVER OCCURS TO THEM. AND UNLESS THE FDA HEARS ABOUT IT, THEY CAN'T SHUT THEM DOWN OR MAKE THEM DO IT.

SO IT'S AN EVOLVING AREA, AND I THINK IT'S GOING TO NARROW THE WINDOW OF THINGS THAT COULD POSSIBLY ESCAPE THE CLINICAL TRIAL REQUIREMENT BECAUSE FOR MOST STEM CELL THERAPIES, AS STEVE AND MICHAEL WERE TALKING ABOUT, EITHER YOU'RE GOING TO WIND UP GIVING THEM RADIOACTIVE TAGS OR YOU'RE GOING TO WIND UP DOING GENETIC ENGINEERING ON THEM OR YOU'RE GOING TO WIND UP ATTACHING THEM TO SCAFFOLDS. I MEAN THERE WILL BE ALL SORTS OF MANIPULATIONS. SETTING ASIDE WHETHER IT'S AUTOLOGOUS AND HOMOLOGOUS, THEY'LL BE MANIPULATIONS THAT ARE GOING TO TRIGGER THE FDA'S OVERSIGHT.

SO IT'S PROBABLY THAT THERE'S SOME NARROW WINDOW OF THINGS HERE THAT STILL MIGHT ESCAPE THE REGULATORY REQUIREMENTS, BUT I THINK IT'S PROBABLY SHRINKING.

DR. WAGNER: NO. NO. NO. BUT WE GET CORD BLOOD FOR EVERYTHING. CORD BLOOD IS BEING INJECTED EVERYWHERE YOU CAN THINK OF, AND IT'S NO MANIPULATION.

DR. CHARO: SO IT'S NOT -- SO IT'S ONLY MINIMALLY MANIPULATED, BUT IT IS NONAUTOLOGOUS.

DR. READ: BUT FOR CORD BLOOD.

DR. CHARO: AND IT'S HOMOLOGOUS.

DR. WAGNER: NO, IT'S NOT HOMOLOGOUS.

DR. CHARO: MAYBE YOU'RE RUNNING INTO TROUBLE.

DR. READ: ANY CORD BLOOD IS STILL A 361 HCTP, SO EVEN IF YOU DON'T HAVE AN IND, YOU'RE STILL SUBJECT TO FDA INSPECTIONS OF THE FACILITY THAT'S PROCESSING IT.

DR. CHARO: BUT THAT'S DIFFERENT FROM REQUIRING AN IND, RIGHT?

DR. READ: RIGHT. RIGHT.

DR. CHARO: BECAUSE NOW YOU'RE TALKING JUST PUBLIC HEALTH SERVICE ACT REQUIREMENTS FOR INFECTION CONTROL.

DR. READ: RIGHT.

DR. CHARO: RIGHT? NOT THE KIND OF DRUG CLINICAL TRIAL EFFICACY SAFETY TRIALS.

DR. READ: RIGHT.

DR. KIESSLING: THERE'S AN UP-AND-COMING TREATMENT FOR RACEHORSES NOW THAT IF YOUR HORSE RACE --

DR. CHARO: I'M SORRY. FOR WHAT?

DR. KIESSLING: FOR RACEHORSES. IF YOUR RACEHORSE HURTS ITSELF, ITS LEG GETS ONE OF THESE HAIRLINE FRACTURES OR SOMETHING, THEY'RE DOING A STERNAL TAP ON THOSE ANIMALS, AND THEY'RE PUTTING THOSE BONE MARROW CELLS BACK INTO THE SITE OF THE

INJURY.

NOW, I DON'T THINK THAT KIND OF A PROCEDURE WOULD, UNDER THE CURRENT GUIDELINES, COME UNDER FDA OVERSIGHT AT ALL.

DR. CHARO: IT'S COMPLICATED. THERE IS A WHOLE SECTION ON ANIMAL DRUGS.

DR. READ: THE VETERINARY, YEAH.

DR. KIESSLING: NO. NO. NO. BUT I MEAN IF IT WORKS, IF YOUR RACEHORSE NOW WINS THE NEXT RACE, THE NEXT TIME AN ATHLETE HURTS HIS ANKLE --

DR. TAYLOR: THEY'RE GOING TO WANT TO TRY IT.

DR. KIESSLING: -- THEY'RE GOING TO WANT TO TRY IT. AND I'M NOT SURE -- IT'S AWFUL. I'M NOT SURE IT SHOULDN'T BE TRIED, BUT I DON'T THINK THAT'S GOING TO COME UNDER FDA PURVIEW.

DR. CHARO: I THINK THE LONG AND SHORT OF IT IS THAT YOU'VE GOT THE RIGHT PERSON ON YOUR STAFF BECAUSE YOU NEED AN FDA GEEK WORKING FULL TIME WITH CIRM, AND APPARENTLY YOU'VE GOT ONE BECAUSE WE'RE THE DUELING GEEKS OVER HERE.

DR. CSETE: WE DON'T OWN HER UNFORTUNATELY.

DR. CHARO: OH, SHE'S AT UCSF. SHE'S NOT WITH YOU.

DR. ROBERTS: E. J., WHAT'S THE ANSWER TO THAT? IS ANN RIGHT, THAT IT WOULD NOT BE COVERED?

DR. READ: YEAH. I'M A LITTLE CONFUSED. I THINK I KNOW -- THE COMPANY'S IN CALIFORNIA, RIGHT?

DR. KIESSLING: I DON'T KNOW.

DR. READ: I'VE HEARD THAT GUY TALK. AND HE'S ACTUALLY BEEN TALKING TO FDA, BUT I THINK HE'S ALLOWED -- I THINK THEY'RE ALLOWED TO SET UP THEIR TRIALS IN ANIMALS. I THINK THEY STILL HAVE TO FOLLOW THE ANIMAL RULES.

DR. KIESSLING: NO. I'M NOT TALKING ABOUT AN ANIMAL. I'M TALKING ABOUT IF YOU DID THAT IN A HUMAN, OKAY, THIS IS NOT MANIPULATED AT ALL. YOU'RE A BASKETBALL PLAYER.

DR. READ: YOU'RE TAKING BONE MARROW AND STICKING IT SOMEWHERE ELSE.

DR. CHARO: YOU MEAN IT'S JUST BASIC MALPRACTICE.

DR. KIESSLING: RIGHT.

DR. READ: AND IT'S AUTOLOGOUS AND IT'S NONHOMOLOGOUS AND YOU'RE ALSO DOING IT SORT OF UNDER ONE ROOF AND IT DOESN'T HAVE TO BE MANIPULATED AND IT'S NOT BEING STORED FOR A FEW DAYS AND SO ON. YEAH, YOU COULD DO THAT. AND THERE ARE SURGEONS WHO

DO TISSUE-TYPE THINGS IN THE O.R. THAT'S OKAY.

DR. KIESSLING: THAT'S JUST LIKE TRANSPLANTING A NERVE FROM SOMEPLACE TO ANOTHER.

DR. READ: BUT I THINK THAT MOST OF THE THINGS THAT CIRM IS DEALING WITH ARE A WHOLE LOT MORE COMPLEX THAN THAT. AND I THINK THAT'S WHAT WE'RE SORT OF TALKING ABOUT.

CHAIRMAN LO: RIGHT. I THINK WITHOUT SORT OF GETTING TOO ENMESHED IN THIS, I THINK WE NEED TO REMIND OURSELVES WE'RE TALKING ABOUT CIRM-FUNDED PROJECTS WHICH HAVE TO GO THROUGH SCIENTIFIC REVIEW AND BE CONSISTENT WITH THE CIRM SCIENTIFIC GUIDELINES. AND IT WOULD CERTAINLY BE SUBJECT TO FDA APPROVAL OVERSIGHT AS IS NEEDED. SO I THINK A LOT OF THIS IN THE U.S. WILL GET SETTLED AS A REGULATORY ISSUE.

AND AS INSU SAID, THE IMPETUS FOR THIS IN THE ISSCR GUIDELINES REALLY CAME FROM THE INTERNATIONAL CONTEXT WHERE COUNTRIES LIKE CHINA AND INDIA DO NOT REGULATE STEM CELL RESEARCH AT ALL AND DO NOT HAVE ANY COMPARABLE FDA PROGRAM FOR CELLULAR THERAPEUTICS. SO I THINK IT'S AN INTERESTING CONCEPTUAL QUESTION, BUT I THINK IN TERMS OF OUR MISSION WITH CIRM, I THINK IT'S PROBABLY NOT GOING TO BE AS BIG AN ISSUE AS IT WAS FOR ISSCR.

DR. HYUN: I HAVE A QUESTION. SO I UNDERSTOOD THAT FDA DOESN'T STEP IN IF IT'S AUTOLOGOUS, MINIMALLY MANIPULATED, BUT IT MIGHT STILL BE NONHOMOLOGOUS. WOULD THEY COME IN BECAUSE IT'S NONHOMOLOGOUS? I THOUGHT AS LONG AS THIS IS MINIMALLY MANIPULATED --

DR. READ: NONHOMOLOGOUS IS CONSIDERED A -- WELL, IT DEPENDS ON WHAT YOU'RE TALKING ABOUT. BUT IF IT MEETS THE DEFINITION OF AN HCTP, A HUMAN CELL TISSUE PRODUCT, AND THERE'S NONHOMOLOGOUS USE, THEN IT IS KICKED UP AND REQUIRES AN IND.

DR. CHARO: I THINK ONE OF THE THINGS THAT --

DR. READ: YOU COULD ARGUE WHAT NONHOMOLOGOUS MEANS, BUT USUALLY --

DR. CHARO: JUST BY WAY OF REFERENCE, I'VE CALLED UP THE PAGE ON FDA, AND I CAN SEND IT OUT TO EVERYBODY, THAT KIND OF LAYS THIS OUT IN A MORE COMPREHENSIBLE WAY. BUT THE MOST IMPORTANT THING FOR PEOPLE TO KEEP IN MIND, INCLUDING THE CORD BLOOD PEOPLE WHO MAY BE OUT OF COMPLIANCE, IS THAT THESE VARIOUS CRITERIA, THEY'RE LINKED BY THE WORD "OR," NOT THE WORD "AND." THAT IS, EITHER IT'S MORE THAN MINIMALLY MANIPULATED OR IT'S FOR A NONHOMOLOGOUS USE OR IT'S NONAUTOLOGOUS, AND THEN ANY ONE OF THOSE

CAN TRIGGER THE FDA'S OVERSIGHT REQUIRING AN IND. AND SO IT MAY BE THAT SOME OF THESE CORD BLOOD PEOPLE SIMPLY HAVE GOTTEN IT WRONG BECAUSE THESE RULES WERE NOT FINALIZED UNTIL 2005.

DR. READ: WELL, AND CORD BLOOD -- YEAH. I DIDN'T GO INTO A LOT OF DETAIL ON CORD BLOOD, BUT CORD BLOOD IS A LITTLE BIT FUNNY. IF IT'S PUBLICLY BANKED CORD BLOOD, IT'S CONSIDERED A 351 HCTP BECAUSE IT'S AN UNRELATED DONOR. BUT UNTIL THAT GUIDANCE GETS FINALIZED REQUIRING THE BANKS TO HAVE LICENSE APPLICATIONS, PEOPLE ARE EITHER DOING THINGS UNDER IND OR NOT BECAUSE THEY HAVE THIS FUNNY IND MORATORIUM. SO THE PEOPLE WHO ARE IN PRACTICE, LIKE JOHN, MAY USE CORD BLOOD FOR SOMETHING OTHER THAN WHAT THAT GUIDANCE SAYS. AND SO FDA IS NOT GOING TO SHUT THEM DOWN, BUT THEY'RE TRYING TO ENCOURAGE THEM TO SUBMIT DATA SO THAT THEY CAN DO THAT LEGALLY.

SO IT'S NOT AN EGREGIOUS OFFENSE BECAUSE THE CORD BLOOD'S ALREADY BEEN BANKED. THEY'RE JUST USING IT IN A SORT OF DIFFERENT INDICATION.

CHAIRMAN LO: I'M GOING TO TRY AND MOVE US ON BECAUSE THERE'S A COUPLE OTHER THINGS I'D LIKE TO DO BEFORE WE ADJOURN. SO ANY OTHER QUESTIONS ON OTHER TOPICS?

DR. PRIETO: JUST ON THIS TOPIC, AND I'M

TRYING TO FIGURE OUT HOW TO SEND IT TO EVERYONE, BUT IN THE *NEW YORK TIMES* TWO DAYS AGO, THERE WAS AN ARTICLE ON TREATMENT CURRENTLY BEING DONE IN HUMANS WHO ARE HAVING THEIR OWN BLOOD, ACTUALLY PLATELET RICH PLASMA INJECTED INTO INJURED TISSUES. SO THIS IS HAPPENING NOT JUST IN RACEHORSES.

DR. READ: RIGHT. RIGHT. AND THAT WAS PLATELET RICH PLASMA FROM THEMSELVES, RIGHT?

DR. PRIETO: FROM THEMSELVES.

DR. READ: SO IT'S AUTOLOGOUS. SO IT'S AN AUTOLOGOUS BLOOD PRODUCT, BUT IT'S AN INTERESTING USE, RIGHT. SO I DON'T KNOW WHAT THE FDA IS SAYING ABOUT THAT ONE.

CHAIRMAN LO: ALL RIGHT. SO I WANT TO TRY AND MOVE US ON. STEVE PECKMAN HAD A COUPLE OTHER ISSUES, AND THEN I WANT TO SORT OF -- ACTUALLY IT'S GOING TO BE FAST, STEVE, BECAUSE AT QUARTER OF ONE, WHICH IS IN ABOUT 15 MINUTES, I WANT TO SORT OF COME BACK TO THE SWG TO SORT OF DO A WRAP-UP AND NEXT STEPS AND SORT OF PLAN WHAT WE DO NEXT. SO, STEVE, I'M GOING TO SQUISH YOU DOWN HERE TO 15 MINUTES OF PRESENTATION AND Q AND A. GEOFF IS GOING TO HELP YOU GET YOUR SLIDES BACK UP.

THANKS, INSU. THAT WAS VERY HELPFUL.

DR. PECKMAN: I WAS WONDERING IF THAT *NEW*

YORK TIMES ARTICLE WAS ABOUT AROD.

DR. CHARO: IT WAS ABOUT ATHLETES ACTUALLY. AROD HAD ALREADY PICKED A DIFFERENT TREATMENT.

DR. PRIETO: THE GENERAL APPROACH TO THIS WAS THAT, YOU KNOW, THERE REALLY WERE NOT ANY ETHICAL QUESTIONS RAISED. THE LEAD SENTENCE IS TWO OF THE PITTSBURGH STEELERS BIGGEST STARS, HINES WARD AND TROY POLAMALU, USED THEIR OWN BLOOD IN AN INNOVATIVE INJURY TREATMENT BEFORE WINNING THE SUPER BOWL. AND I THINK YOU ALL HAVE THE LINK NOW.

CHAIRMAN LO: I'LL ASK STEVE TO TURN DOWN HIS PRESENTATION OR JUST TAKE THE HIGHLIGHTS.

DR. PECKMAN: THIS IS AS FAST AS I CAN GO, THOUGH.

DR. CHARO: BUT LOOK HOW WELL WE CAN ALL READ IT DESPITE THOSE LITERACY RATES.

DR. PECKMAN: CLEARLY YOU SPEND MORE THAN SEVEN MINUTES A DAY READING, ALTA.

DR. CHARO: ACTUALLY DOROTHY POINTED OUT THAT MOST OF THOSE TEENAGERS ARE SPENDING 14 HOURS A DAY READING TEXT MESSAGES.

DR. PECKMAN: WHICH AREN'T WRITTEN IN ENGLISH. THEY'RE WRITTEN IN SOME SUBFORM.

SO WE'VE GONE THROUGH THE PROCESS OF WHAT

IT TAKES TO GET IT REVIEWED, AND THEN WHAT ARE WE DOING TO ENSURE THAT HUMAN SUBJECTS ARE PROTECTED ONCE THEY ENROLL IN THE TRIAL. WELL, THERE'S A WHOLE LOT OF POSTAPPROVAL MONITORING GOING ON THAT IRB'S AND OTHER COMMITTEES ARE INVOLVED IN. IN FACT, REGULATIONS REQUIRE ONGOING REVIEW OF RESEARCH. SOME PEOPLE BELIEVE THIS IS JUST A PAPER REVIEW THAT HAPPENS ANNUALLY, BUT ACTUALLY IN MUCH RESEARCH IT HAPPENS MORE THAN THAT. AND FDA IS VERY MUCH ENCOURAGING IT TO HAPPEN MORE THAN JUST ANNUALLY.

SO WHAT WE HAVE IN TERMS OF POSTAPPROVAL MONITORING IS THE RESPONSIBILITY TO REVIEW WHAT INSU TALKED ABOUT WAS ADVERSE REACTIONS OR UNEXPECTED EVENTS. IN FACT, IF CIRM IS GOING TO FUND CLINICAL TRIALS, CIRM WILL BE ACTING AS A SPONSOR AND WILL BE RECEIVING ADVERSE EVENTS AND WILL HAVE TO TALLY THEM AND ENSURE THAT APPROPRIATE DATA IS DISSEMINATED. SO THERE'S A REPORTING AND RECEIVING REQUIREMENT THAT GOES ALONG WITH THAT. SO IRB'S ARE A PART OF THAT BECAUSE THEY ACTUALLY RECEIVE THESE EVENTS AND EVALUATE THEM AS WELL.

ANOTHER FORM OF POSTAPPROVAL MONITORING IS AN ISSUE THAT I THINK IS NEAR AND DEAR TO MOST PEOPLE'S HEARTS, AS I HEARD FROM THE DISCUSSION

EARLIER, IS HOW DO WE KNOW THAT THE INFORMED CONSENT PROCESS IS ACTUALLY WORKING? AND THE FEDERAL REGULATIONS ACTUALLY PROVIDE THE IRB WITH THE AUTHORITY TO OBSERVE OR HAVE A THIRD-PARTY OBSERVER PARTICIPATE IN THE CONSENT PROCESS. AND ACTUALLY HAVING DONE THAT MYSELF MANY TIMES AS A CONSENT ADVOCATE OR MONITOR, I CAN TELL YOU IT'S QUITE TELLING. AND, IN FACT, IT CAN SERVE TO EMPOWER AND FACILITATE DECISION-MAKING OF SUBJECTS, HELPING THEM HELP THEMSELVES. IT ALSO HELPS INVESTIGATORS AS WELL. IT HELPS EVERYONE UNDERSTAND RISK-BENEFIT RATIOS, AND IT ALSO CAN ADDRESS COMPETENCY CHANGES.

I'LL TELL YOU ONE SHORT STORY SINCE BERNIE NEEDS TO GET MOVING ON ANOTHER AGENDA ITEM. CLINICAL TRIAL ON PARKINSON'S DISEASE, WHICH WAS AN INVESTIGATIONAL DRUG DELIVERED BY AN INVESTIGATIONAL DEVICE DIRECTLY INTO THE BRAIN IN A RANDOMIZED CONTROL FASHION. THE IRB WAS SERIOUSLY CONCERNED THAT PARKINSON'S PATIENTS DESPERATE FOR HELP WITH THEIR DISEASE WOULD ENROLL IN THIS TRIAL WITHOUT SERIOUSLY CONSIDERING AND MAKING KNOWLEDGEABLE DECISIONS.

SO I WAS THE CONSENT ADVOCATE OR MONITOR FOR THAT TRIAL. AND AT OUR INSTITUTION THERE WERE FIVE OR SIX PATIENTS WHO WANTED TO ENROLL OF WHICH

ONE DID. CONSENT PROCESS ON AVERAGE WAS AN HOUR AND A HALF PER SUBJECT, OF WHICH MOST OF IT WAS DISCUSSION ABOUT RISKS AND BENEFITS OF PARTICIPATION IN RESEARCH, WHAT IT MEANT TO BE IN A RANDOMIZED CLINICAL TRIAL. CLEARLY THIS WAS JUST ANECDOTAL INFORMATION, BUT I HAVE MANY SIMILAR STORIES TO TELL ABOUT MANY OTHER TYPES OF RESEARCH PROJECTS FOR BOTH DECISIONALLY COMPROMISED PATIENTS AND THOSE WHO WERE NOT, BUT YET VERY EAGER TO PARTICIPATE IN RESEARCH.

SO MONITORING CONSENT CAN CERTAINLY CONSIST OF THE IRB DESIGNATING AN ADVOCATE SERVE ON BEHALF OF THE SUBJECTS, AND THE MONITORER OR ADVOCATE DOES MORE -- CAN DO MORE THAN JUST SIT THERE. THEY COULD BE PASSIVE, IT COULD BE A SINGULAR EVENT, OR IT COULD BE AN ONGOING PROCESS AND POSTSIGNING WHICH WE HAVE DONE AS WELL.

SO THIS IS ENSURING THAT INFORMED CONSENT IS A PROCESS RATHER THAN THE SIGNING OF A DOCUMENT MUCH LIKE A CONTRACT WHEN YOU BUY YOUR CAR. THAT'S WHAT WE WANT TO AVOID. WE WANT TO ENSURE PROCESS-ORIENTED DECISION-MAKING.

WE LISTEN AND OBSERVE THE CONSENT AND THE PROCESS, THE COMMUNICATION WITH THE INVESTIGATOR AND THE SUBJECT AND THE SUBJECT'S FAMILY, AND WE ASK QUESTIONS. WE'RE KNOWLEDGEABLE ABOUT THE PROTOCOL,

THE SCIENCE, AND THIS IS IN ORDER TO FACILITATE COMPREHENSION. AND WE ELICIT QUESTIONS FROM BOTH THE INVESTIGATOR AND THE SUBJECT. AND CLEARLY WE ALSO DOCUMENT PEOPLE'S UNDERSTANDING WITH MORE THAN YES-NO QUESTIONS, BUT QUESTIONS THAT REQUIRE NARRATIVE RESPONSES.

THE MONITOR ADVOCATE DETERMINES UNDERSTANDING AND, IF NECESSARY, REQUESTS THAT THE INVESTIGATOR REREVIEW MATERIALS WITH THE SUBJECT. IF THE MONITOR DOES NOT THINK THE SUBJECT UNDERSTANDS THE RESEARCH OR ALL ITEMS IN THE CONSENT DOCUMENT, THEN THE SUBJECT IS NOT ENROLLED IN THE RESEARCH. AND ALL CONSENT ENCOUNTERS ARE REPORTED TO THE IRB.

IS IT WORTH IT? WELL, IT CHANGES BEHAVIOR. ANECDOTALLY I CAN TELL YOU INVESTIGATORS HAVE CHANGED HOW THEY APPROACH THE CONSENT PROCESS AND HAVE SHARED WITH ME HOW IT'S FUNDAMENTALLY CHANGED THEIR APPROACH AFTER ENGAGING THROUGH AND ADVOCATE OR CONSENT MONITOR. IT ASSURES THE IRB THAT CONSENT IS ACTUALLY A PROCESS WITH KNOWLEDGEABLE DECISION-MAKING, AND IT MAY ADDRESS SOME ETHICAL ISSUES, ALTHOUGH IT MAY CREATE SOME AS WELL. DOES IT FACILITATE OR IMPEDE AUTONOMY?

POSTAPPROVAL MONITORING ALSO INCLUDES A

RESEARCH PLAN OF MONITORING THE DATA, WHICH WAS ALLUDED TO EARLIER, THROUGH DATA SAFETY MONITORING BOARDS WHICH INITIATE THROUGH DATA SAFETY MONITORING PLANS. HOWEVER, MUCH OF THESE ARE NOT REAL-TIME MONITORING, AND IT POSES THE QUESTION, ESPECIALLY IN CELLULAR ARTICLES, WHETHER THERE SHOULD BE LONG-TERM FOLLOW-UP SUCH AS IN GENE TRANSFER THAT COULD LAST A LIFETIME. SO MAYBE WHEN YOU ENROLL IN THE PROJECT, YOU SHOULD BE ENROLLED FOR LIFE, AND THERE SHOULD BE PERIODIC REVIEWS OF YOUR STATUS AND HOW THIS MANIPULATION HAS CONTRIBUTED TO OR CHANGED YOUR LIFE. AND MAYBE AFTER COLLECTION OF CERTAIN AMOUNT OF DATA AGREED UPON BY THE SCIENTIFIC COMMUNITY, THAT BECOMES MODIFIED. THERE'S CERTAINLY A LOT OF CANCER AND GENE TRANSFER TRIALS PATIENTS ARE FOLLOWED -- PATIENT SUBJECTS ARE FOLLOWED FOR LIFE.

SO WHAT DOES IT DO? WELL, IT PLAYS AN ESSENTIAL ROLE IN PROTECTING SUBJECTS AND ASSURING THE INTEGRITY OF THE RESEARCH IN THAT WHAT HAS BEEN IN EXISTENCE FOR MORE THAN 30 YEARS AS AN IDEA, IT'S OPERATED BY SPONSORS, INVESTIGATORS, AND IRB'S, THERE ARE CONFLICT OF INTEREST PROCEDURES TO MINIMIZE EVALUATION BIAS, THEY DEVELOP PROTOCOL-SPECIFIC MONITORING GUIDELINES. SO EACH ONE IS INDIVIDUALLY CREATED TO ADDRESS THAT

PROTOCOL'S SITUATION. AND IT PROVIDES AN INTERIM EVALUATION OF DATA AS IT IS CREATED TO THE SPONSOR.

NOW, IT COULD ALSO BE DONE WHERE IT'S REPORTED DIRECTLY TO THE IRB. I'VE DONE THAT AS WELL. AND INTERIM ANALYSES ARE PERFORMED TO ASSESS SAFETY, EFFICACY, AND DATA INTEGRITY.

SO THIS IS THE WAY WE ENSURE THAT THROUGHOUT THE PROCESS OF ADMINISTERING NOVEL CELLULAR ARTICLES TO SUBJECTS, WE UNDERSTAND WHAT THE ONGOING RISK IS AND ARE ABLE TO EVALUATE THOSE RISKS IN TIME TO TRY TO MINIMIZE THEM FOR THE SUBJECTS WHO ARE RECEIVING THEM AND FOR THOSE WHO MAY COME LATER.

SO THE DSMB, THE MONITORING BOARD, WILL REVIEW ADVERSE EVENT REPORTS AS WELL. AND THEY'LL MONITOR AND MAKE RECOMMENDATIONS REGARDING ADDITIONAL ENROLLMENT OF SUBJECTS, MODIFICATION OF STUDY PROCEDURES, ADHERENCE TO THE PROTOCOL; AND AS TOXICITIES ARISE, ANALYZING THEM AND EVALUATING THEM WITHIN THE CONTEXT OF THE RESEARCH AND, AGAIN, ENGAGING IN A RISK-BENEFIT CALCULUS.

THEY HAVE THE AUTHORITY TO SUSPEND OR RECOMMEND EARLY TERMINATION OF THE RESEARCH DUE TO SAFETY CONCERNS, INADEQUATE PERFORMANCE, OR ACCRUAL, OR MAYBE EVEN MORE IMPORTANTLY THAT THE RESEARCH

OBJECTIVES HAVE BEEN ATTAINED OR THEY'RE UNATTAINABLE. BECAUSE CLEARLY IF YOU'VE ATTAINED THE OBJECTIVES, THERE'S NO REASON TO CONTINUE WITH THE RESEARCH. AND IF YOU'VE DISCOVERED THROUGH THIS DATA ANALYSIS THAT YOUR OBJECTIVES ARE UNATTAINABLE, THEN YOU SHOULD STOP AND NOT PLACE ANYONE ELSE AT RISK.

NOW, THIS COULD HAPPEN IN TERMS OF LARGE TRIALS OR SMALL TRIALS, PHASE I OR PHASE III. I CAN TELL YOU I HAVE EXPERIENCE WITH A PHASE I ONCOLOGY PROTOCOL WHERE THERE WERE TEN SUBJECTS FOR PHASE I, NOVEL ARTICLE. OF THOSE -- ALL TEN SLOTS WERE FILLED. A SUBJECT DIED RELATED TO THE RESEARCH. THE DSMB SAID THE STUDY SHOULD BE CLOSED DOWN. THE IRB WANTED TO EVALUATE THE OTHER NINE SUBJECTS. OF THOSE NINE SUBJECTS, ONE SAW SERIOUS IMPROVEMENT WHILE ON THE TRIAL, MORE THAN 75 PERCENT DECREASE IN TUMOR GROWTH. WAS THAT A RESULT OF THE DRUG? WAS IT A RESULT OF SOMETHING ELSE THAT WAS GOING ON? MAYBE PRAYERS WERE ANSWERED. WE DIDN'T KNOW.

SO WE CREATED AN ADDITIONAL MONITORING BOARD WITH A MONITORING TASK THAT HAPPENED IN REAL-TIME BECAUSE WE UNDERSTOOD WHY THE SUBJECT DIED. AND WE FELT THAT SINCE WE DIDN'T KNOW WHETHER THE REMAINING SUBJECT WHO HAD IMPROVED DURING THE

TRIAL, I CAN'T SAY THAT SHE BENEFITED FROM THE TRIAL, BUT HAD IMPROVED DURING THE TRIAL, WHETHER SHE COULD MAINTAIN ON THE TRIAL WITH ADDITIONAL MONITORING TO MINIMIZE THE RISK TO ENSURE THAT THE TRIAL WAS SHUT DOWN IF THE RISKS STARTED TO INCREASE SO THAT SHE DIDN'T HAVE DIMINISHED QUALITY OF LIFE IN HER REMAINING TIME.

THESE ARE ALL PATIENTS WHO WERE VERY ILL WITH CANCER. SO SHE STAYED ON THE TRIAL FOR ANOTHER THREE MONTHS WHILE WE HAD WEEKLY MONITORING OF ALL DATA AS BLOOD COUNTS AND OTHER TESTS WERE PERFORMED TO ENSURE HER SAFETY. AND AT THE POINT WHERE THE DRUG CONTINUED TO ACCUMULATE IN HER BODY WHERE WE KNEW IT WOULD NOT BE RELIEVED, SHE WAS WITHDRAWN FROM THE STUDY BECAUSE WE KNEW IF SHE CONTINUED IN THE STUDY, THE DRUG WOULD CONTINUE TO BUILD UP AND IT WOULD KILL HER. SHE LIVED ANOTHER SIX MONTHS.

SO WE'RE ABLE TO ENSURE SAFETY IN THE TRIAL, MINIMIZE RISK, MAINTAIN OPTIMAL QUALITY OF LIFE, AND STOP THE TRIAL WHEN APPROPRIATE THROUGH ONGOING MONITORING. AND THIS IS SOMETHING THAT IRB'S AND MONITORING BOARDS DO ALL THE TIME.

SO THE POINT IS TO TRY TO ASSURE YOU THAT THERE IS INFRASTRUCTURE, PROCESSES, AND PROCEDURES ALREADY IN PLACE THAT YOU DO NOT HAVE TO REINVENT.

AND AS INSU SAID, THERE MAY BE SOME SPOKES NEEDED OR THERE MAY NEED TO BE SOME WAX ON THE WHEELS IN ORDER TO MAKE THEM RUN MORE SMOOTHLY. THERE ARE A LOT OF THINGS IN PLACE TO ENSURE THE PROTECTION OF SUBJECTS.

HOWEVER, THE DSMB SHOULD ALWAYS INFORM THE IRB OF OPERATING PROCEDURES. DO IRB'S REQUEST DSMB REPORTS? IF NOT, THEY SHOULD. ARE THE REPORTS VALUABLE? ABSOLUTELY. THE PROBLEM IS THE HISTORY OF DSMB'S HAS BEEN A LITTLE UNEVEN AND THAT THE REAL-TIME RELATIONSHIP TO THESE ANALYSES PROBABLY SHOULD BE INCREASED IN NOVEL APPROACHES WITH HUMANS.

ADDITIONALLY, DSMB'S SHOULD DO MORE IN THEIR REPORTS THAN THEY COMMONLY DO WITH INDUSTRY SPONSORS, WHICH IS REPORT TO IRB'S THAT THINGS ARE GOING WELL. THEY ALSO HAVE TO REPORT WHEN THEY'RE NOT GOING WELL. IT'S THE KIND OF NEGATIVE FINDINGS RESULT YOU'RE TALKING ABOUT AT THE END OF THE TRIAL. CHANGES IN THE DSMB SHOULD ALWAYS BE REPORTED AS WELL.

LONG-TERM FOLLOW-UP, AS I NOTED BEFORE, NOVEL CELL-BASED RESEARCH MAY NEED TO HAVE LONG-TERM FOLLOW-UP WITH SUBJECTS TO ENSURE SAFETY OF CURRENT AND FUTURE RECIPIENTS OF PRODUCTS AND TO MAXIMIZE GENERALIZED KNOWLEDGE. LONG-TERM FOLLOW-UP ABOUT

QUALITY OF LIFE, HOW DOES IT CHANGE, IF IT CHANGES AT ALL. LIFETIME FOLLOW-UP IS COMMON IN GENE TRANSFER RESEARCH, AND THE ISSCR GUIDELINES SEEM TO IMPLY A NEED FOR THIS AS WELL.

AND MY FINAL POINT FOR THE DAY IN REINVENTING THE WHEEL OR NOT REINVENTING THE WHEEL IS WHAT IS THE ROLE OF THE SCRO IN ALL OF THIS? I STARTED OUT THE TALK TODAY BY NOTING THAT THE SCRO'S ESSENTIALLY WERE IDEALIZED AND CONCEPTUALIZED BY THE NATIONAL ACADEMY AS A WAY TO ADDRESS PRECLINICAL RESEARCH. AND CIRM ADOPTED THOSE GUIDELINES AND ADOPTED THE SCRO MODEL AND, AGAIN, TO ADDRESS PRECLINICAL RESEARCH.

SO WHAT IS THE ROLE OF THE SCRO IN THE REVIEW OF CLINICAL RESEARCH? IF IRB'S AND SCIENTIFIC REVIEW COMMITTEES ALREADY EXIST AT INSTITUTIONS IN ORDER TO ASSESS THE RESEARCH AND ARE REQUIRED TO HAVE APPROPRIATE AND ADEQUATE SCIENTIFIC REPRESENTATION, THEN THE SCRO MAY BE REDUNDANT. AND IF IT'S REDUNDANT, DO WE WANT TO PLACE ANOTHER IMPEDIMENT IN THE WAY THAT'S UNNECESSARY IN ORDER TO PROTECT HUMAN SUBJECTS AND TO MAXIMIZE RESEARCH? I DON'T THINK ANYONE IN THIS ROOM IS GOING TO TELL YOU THAT THE RESEARCH WHEEL MOVES FAST ENOUGH DURING THE REVIEW PROCESS. PATIENT ADVOCATES, SCIENTISTS,

PHYSICIANS, AND OTHERS ALL HAVE THE SAME COMPLAINTS. THE WHEEL MOVES TOO SLOW. AND IS THIS ADDITIONAL NEW COMMITTEE NECESSARY IN ORDER TO MAXIMIZE PROTECTION OF SUBJECTS AND TO ENSURE SOUND SCIENCE?

SO IT'S JUST A BRIEF REVIEW OF MEMBERSHIP. THE SCRO CLEARLY HAS TO HAVE SCIENTIFIC EXPERTISE, BUT SO DOES THE IRB AS WOULD A SCIENTIFIC PEER REVIEW COMMITTEE. THE SCRO DOESN'T NEED TO HAVE MEDICAL CLINICAL TRIAL EXPERTISE WHILE THE OTHERS DO. THOUGH THE SCRO IS REQUIRED TO HAVE ETHICS EXPERTISE, IT CERTAINLY IS IMPLIED WITH IRB'S AND IT'S UNNECESSARY FOR SCIENTIFIC PEER REVIEW. COMMUNITY MEMBERSHIP, DIVERSITY OF MEMBERSHIP ARE ALL PARTS OF CERTAINLY THE IRB. SCRO'S ARE NOT REQUIRED TO HAVE BIOSTATISTICIANS BECAUSE IT'S UNNECESSARY FOR LABORATORY RESEARCH. TYPICALLY IRB'S HAVE PHARMACISTS AND RESEARCH NURSES AS PART OF THEIR REVIEW BOARD, AND THEY'RE PART OF THE CLINICAL TRIAL PROCESS.

SO I ASK CIRM TO EVALUATE WHAT THE ROLE OF THE SCRO IS; AND IF IT SHOULD BE MAINTAINED, TO OPTIMIZE IT SO IT HAS VALUE RATHER THAN TO MAKE IT A REDUNDANT BURDEN ON A PROCESS THAT I THINK EVERYONE INVOLVED SAYS ALREADY MOVES TOO SLOW.

SO IN SUMMARY, THERE'S A WELL-ESTABLISHED

CLINICAL RESEARCH REVIEW REQUIREMENT AND OVERSIGHT IN THIS COUNTRY. IT INCLUDES VARIOUS COMPLIANCE COMMITTEES WHICH I TALKED ABOUT, AND THEY'RE GOVERNED BY FEDERAL AND STATE REGULATIONS AS WELL AS INSTITUTIONAL POLICIES. IRB'S ARE KIND OF THE HUB OF THAT WHEEL AROUND WHICH ALL OF THIS SPINS. AND THEY'RE REQUIRED TO HAVE SUFFICIENT SCIENTIFIC EXPERTISE TO EVALUATE THE RESEARCH AND PROTECT THE SUBJECTS. THEY'RE THERE TO MINIMIZE RISKS AND MAXIMIZE BENEFITS. THEY'RE THERE TO ENSURE RESPECT FOR THE DIGNITY AND AUTONOMY OF THE SUBJECTS AND TO ENSURE FAIR SUBJECT SELECTION. AND THEY'RE REQUIRED TO MONITOR THE RESEARCH IN AN ONGOING WAY INCLUDING THE INFORMED CONSENT PROCESS.

THERE IS ROOM FOR IMPROVEMENT, AS I NOTED WITH DATA SAFETY MONITORING BOARDS. AND IT'S IMPORTANT TO EVALUATE AND MINIMIZE REDUNDANCY OF THE SCRO. BECAUSE IN THE WORDS OF MY FAVORITE ROMANTIC POET, ABOUT 500 YEARS -- THREE HUNDREDS YEARS AGO, "WHAT IS NOW APPROVED WAS ONCE ONLY IMAGINED." AND THIS IS OUR FUTURE. AND THE FUTURE MEANS A GREAT DEAL TO EVERYONE IN THIS ROOM AND OUTSIDE OF THIS ROOM AND IT NEEDS TO BE SUCCESSFUL. SO THANK YOU VERY MUCH.

CHAIRMAN LO: OKAY. THANKS. I WANT TO

HAVE JUST A COUPLE MINUTES, LIKE MAYBE THREE OR FOUR COMMENTS AND QUESTIONS BECAUSE I WANT TO TRY AND GET SORT OF A WRAP-UP AND NEXT STEPS. SO ALTA, ANYBODY HAVE A COMMENT THEY WANT TO MAKE? QUICK COMMENTS AND RESPONSES.

DR. CHARO: VERY QUICK, JUST AGAIN FOR THE RECORD, ON THE ASSUMPTION THAT NIH IS ABOUT TO BEGIN FUNDING AGAIN IN THIS AREA, JUST A COUPLE OF THINGS TO KEEP IN MIND WITH REGARD TO THE ESCRO, SCRO'S, HOWEVER YOU WANT TO CALL THEM. FIRST, NIH CANNOT REQUIRE THAT THEY BE USED BECAUSE THEY ARE NONGOVERNMENTAL AND, THEREFORE, NIH IS GOING TO HAVE TO COME UP WITH ITS OWN GUIDELINES FOR WHAT WILL OR WILL NOT BE FUNDED OR HOW IT WILL BE CONDUCTED WITH FEDERAL FUNDING. SO I THINK WE NEED TO STAY TUNED FOR THE NEXT DEVELOPMENT IN TERMS OF WHETHER INSTITUTIONS ARE GOING TO KEEP THEIR SCRO'S OR ABANDON THEM ENTIRELY IN THE CONTEXT OF PRECLINICAL WORK. AND NOBODY KNOWS HOW THAT'S GOING TO TURN OUT.

SECOND, THAT THE NATIONAL ACADEMIES COMMITTEE THAT IS KIND OF THE ONGOING COMMITTEE WITH REGARD TO THOSE SCRO'S RECENTLY DID A SURVEY AROUND THE COUNTRY OF PEOPLE'S ATTITUDES ABOUT THEM AND WHETHER THEY HAD CONTINUING VALUE. THOSE RESULTS

ARE PUBLIC. IF YOU HAVEN'T GOTTEN THEM OR WOULD LIKE TO GET THEM, SEND A NOTE TO THE NATIONAL ACADEMIES TO FRAN SHARPLES. YOU WILL GET THEM.

IT WAS VERY INTERESTING. THERE WAS A KIND OF GENERAL VIEW THAT THERE WAS SOME VALUE IN THEM, BUT THERE WERE CERTAINLY SOME PEOPLE WHO WERE PRETTY EXPLICIT ABOUT THEIR DESIRE TO GET RID OF ANY REDUNDANCIES. SO YOU MIGHT BE ABLE TO FIND SOMETHING USEFUL THERE TO THINK ABOUT WHAT TO DO WITHIN YOUR OWN INSTITUTION.

MR. SHESTACK: WHAT WOULD THE PRACTICAL IMPLICATION OF THAT BE FOR CIRM?

DR. CHARO: WELL, FOR CIRM IT HAS THE COMPLICATION THAT MUCH OF WHAT CIRM SAYS YOU MUST DO HAS NOW BEEN ADOPTED IN ADMINISTRATIVE REGULATION UNDER CALIFORNIA LAW WHICH CAN'T BE CHANGED WITHOUT ANOTHER FORMAL ADMINISTRATIVE PROCESS. SO FOR CIRM THERE ARE REVIEW PROCESSES THAT ARE IN PLACE AND MUST STAY IN PLACE REGARDLESS OF WHAT NIH DOES, AND IT'S GOING TO, I THINK, ADD YET ANOTHER LAYER TO THIS ANNOYING PROBLEM OF DIFFERENT RULES APPLYING DEPENDING UPON WHERE YOU GET YOUR FUNDING, AND YET THE SAME LABORATORY MAY BE GETTING FUNDING FROM THREE DIFFERENT SOURCES, CIRM, NIH, PRIVATE. SO YOU'VE GOT THE CALIFORNIA STATE LAW, YOU'VE GOT THE

CIRM REGULATIONS, AND YOU WILL HAVE THE NIH GUIDELINES, AND I WOULD IMAGINE IN THE MIX THERE THAT AT ONE POINT NATIONAL ACADEMIES VOLUNTARY GUIDELINES MIGHT GET DROPPED JUST AS ONE THING YOU CAN DROP WITHOUT A FORMAL ACTION. BUT --

MR. SHESTACK: THIS WOULD BE A QUESTION FOR YOU, ALAN. WILL THERE BE SORT OF ONGOING DISCUSSION WITH NIH AS THOSE STANDARDS DEVELOP FOR THE FORESEEABLE FUTURE? WE WILL STILL BE FUNDING MORE STEM CELL RESEARCH THAN THEY WILL?

DR. CHARO: BEFORE ALAN ANSWERS, JUST TO BE VERY CLEAR, NIH WILL NOT BE ABLE TO FUND DERIVATIONS BECAUSE THAT WOULD STILL VIOLATE.

MR. SHESTACK: WILL --

DR. CHARO: -- DERIVATIONS OF NEW LINES BECAUSE THAT WOULD STILL VIOLATE DICKEY-WICKER. THEY CAN ONLY FUND WORK ON LINES THAT WERE DERIVED WITH NONFEDERAL MONEY. SO THERE WILL ALWAYS BE A PLACE FOR FORMAL ADMINISTRATIVE RULE OR VOLUNTARY GUIDELINES WITH REGARD TO THE DERIVATION PROCESS, THE RECRUITMENT OF DONORS FOR EGGS, FOR SPERM, FOR EMBRYOS, FOR SOMATIC CELLS, AND THE CREATION OF NEW LINES. THAT'S NOT GOING TO GO AWAY RIGHT AWAY.

BUT UNTIL NIH GOES THROUGH THE PUBLIC CONSULTATION PROCESS TO DRAFT ITS OWN GUIDELINES,

IT'S GOING TO BE VERY HARD TO PREDICT EXACTLY HOW CLOSE THEY'RE GOING TO MATCH THOSE THINGS THAT PEOPLE ARE ALREADY DOING IN TERMS OF BOTH PROCESS AND SUBSTANCE.

CHAIRMAN LO: I THINK THIS IS SOMETHING WE NEED TO KEEP OUR EYES PEALED TO BECAUSE IT'S CERTAINLY GOING TO CHANGE OVER THE NEXT ONE TO TWO YEARS. ANY OTHER?

SO WHAT I HEARD TODAY -- FIRST OF ALL, THANKS TO ALL FOR TWO DAYS OF VERY SORT OF STIMULATING, WIDE-RANGING, GOOD DISCUSSION. I THINK I WANT TO SORT OF GO BACK TO WHAT SHERRY HAS BEEN SAYING SINCE WE FIRST CONVENED. AND THAT'S OUR ROLE TO TRY AND SORT OF THINK ABOUT THE MOST DIFFICULT, COMPLICATED ISSUES AND MAKE SURE THAT CIRM REALLY ADDRESSES ALL THE ETHICAL ISSUES INVOLVED IN THE RESEARCH IT FUNDS SO THAT THE PEOPLE OF CALIFORNIA CAN BE CONFIDENT THAT WE HAVE THOUGHT ABOUT THE ISSUES AND MAKE SOME SENSIBLE RECOMMENDATIONS.

WE HAVE HEARD CHALLENGES TODAY THAT WITH CLINICAL TRIALS THERE'S A NEW SET OF SCIENTIFIC ISSUES, BUT A NEW SET OF ETHICAL AND POLICY ISSUES. AND I THINK A COUPLE OF OUR SPEAKERS PUT IT VERY WELL, THAT WE DON'T WANT TO TRY AND REINVENT THE WHEEL; BUT WHERE THE WHEEL CAN BE IMPROVED OR WHERE

WE CAN ADD A SPOKE, WE SHOULD CERTAINLY THINK ABOUT DOING THAT.

SO LISTENING TO THE DISCUSSION TODAY, IF GEOFF CAN FIND THE SLIDE, IT'S THE VERY LAST ONE, THERE WERE MAYBE FOUR THINGS THAT I HEARD AS IDEAS TO PURSUE. AND MY PROPOSAL IS THAT WE NOT DO ANY FORMAL VOTING, BUT THAT WE IDENTIFY ISSUES THAT WE WANT GEOFF AND STAFF TO THINK MORE ABOUT IN CONJUNCTION WITH ALAN AND MARIE. AND WHAT GEOFF HAS DONE IN THE PAST FOR US IS ON DIFFERENT ISSUES PREPARED POLICY BRIEFS WHERE HE LAYS OUT DIFFERENT OPTIONS FOR ADDRESSING THE ISSUE, MAYBE PROVIDES MORE BACKGROUND, AND ALSO THE ARGUMENTS FOR AND AGAINST DIFFERENT OPTIONS. SO TO KIND OF LET US TAKE THE NEXT STEP IN KIND OF THINKING ABOUT WHAT, IF ANYTHING, MIGHT WE WANT TO RECOMMEND ON THESE FOUR ISSUES.

SO LET ME GO FROM THE BOTTOM BECAUSE WHAT I HEARD TODAY WAS A LOT OF CONCERN ABOUT WANTING TO HAVE A WAY OF PROVIDING FREE CARE TO PARTICIPANTS WHO SUFFERED INJURY AS, ALTA, IT WOULD BE DIRECT AND PROXIMATE COMPLICATIONS OF PARTICIPATING IN A CLINICAL TRIAL AT NO COST TO THEM.

GOING BACK UP TO NO. 3, SOME DISCUSSION OF WHETHER WE SHOULD, THIS IS, AGAIN, FOR ONLY

CIRM-FUNDED RESEARCH, IN CLINICAL TRIALS CALL FOR SOME ASSESSMENT OF COMPREHENSION OF PARTICIPANTS, THAT THEY UNDERSTAND THE KEY ASPECTS OF THE TRIAL SO THEY'RE REALLY INFORMED.

SECOND, A TIMELY DISCUSSION BY CIRM-FUNDED RESEARCHERS OF FINDINGS OF CLINICAL TRIALS INCLUDING NEGATIVE RESULTS. AND THIS ISSUE WILL BE COMPLICATED BECAUSE WE HEARD A LOT OF CAUTIONS THAT SOME COMPANIES WOULD BE VERY CONCERNED ABOUT DISCLOSING PROPRIETARY INFORMATION, TRADE SECRETS THAT GIVE THEM A COMPETITIVE ADVANTAGE WHICH THEY WANT TO MAINTAIN. SO THIS WOULD BE PERHAPS A DILEMMA BECAUSE THERE ARE REASONS TO WANT DISSEMINATION OF THOSE FINDINGS, BUT ALSO CONCERNS THAT INSISTING ON THEM MAY ACTUALLY DETER COMPANIES FROM ENTERING INTO TRIALS FUNDED BY CIRM.

AND THE FIRST ONE ON THE LIST WHICH I THINK WE NEED A LITTLE MORE CLARIFICATION OF IS CONVENING SOME SORT OF CONSENSUS MEETING INVOLVING SCIENTISTS AS WELL AS FDA, IF THAT'S POSSIBLE, TO HELP CLARIFY WHAT THE STANDARDS WILL BE FOR PRECLINICAL REQUIREMENTS FOR FDA APPROVAL. AND THIS GOES BACK, I THINK, TO WHAT -- I'M TRYING TO REMEMBER. SOMEBODY OVER ON THE LEFT THERE SAID YESTERDAY, I THINK IT WAS JOSE, THAT IF HE SUBMITS A

PROTOCOL TO FDA, HE CAN'T CALL UP FDA AND SAY I'M THINKING ABOUT DOING A STEM CELL STUDY ON DISEASE X WITH THIS KIND OF STEM CELLS. GIVE ME SOME IDEA OF WHAT I'M GOING TO BE REQUIRED TO DO BASED ON WHAT YOU'VE SEEN AND YOUR EXPERIENCE.

AS MARIE HAS POINTED OUT, THAT THEY CANNOT DISCLOSE CONFIDENTIAL INFORMATION, AND SO WHAT THEY'LL SAY IS SEND US A PROPOSAL AND WE'LL GET BACK TO YOU AS TO WHETHER WE THINK IT'S ACCEPTABLE. THAT MAY NOT BE THE MOST EFFICIENT WAY OF DOING IT. AND SO THE GOAL OF THESE KIND OF MEETINGS WOULD BE JUST TO SORT OF DEVELOP A CONSENSUS STANDARD IN THE FIELD.

NOW, I KNOW THAT ALTA ALREADY HAS IDEAS FOR CONVENING SUCH A MEETING THROUGH THE UNIVERSITY OF WISCONSIN MADISON.

DR. CHARO: WE'RE WAITING FOR A RESPONSE FROM THE FDA.

CHAIRMAN LO: AND THEN I THINK UCI AND THE UCSD, IS THAT RIGHT, ARE THINKING ABOUT THIS AS WELL. SO I THINK THERE'S SOME OTHER INTEREST IN THIS.

I THINK I ALSO HEARD SOME CONCERNS ABOUT SORT OF WHAT EXACTLY WOULD BE THE END POINT, BUT I THINK -- I WANT TO MAKE SURE THESE WERE THE ISSUES

WE THOUGHT WE SHOULD TRY AND WORK ON AND TRY AND CLARIFY, SPECIFY WHAT THESE WOULD BE, AND TO COME BACK THROUGH E-MAIL AND OUR NEXT MEETING FOR MOVING AHEAD.

MS. LANSING: I JUST WANT TO REEMPHASIZE WHAT I THINK OUR ROLE IS, AND BACK TO ALAN AND GEOFF AND MARIE AND EVERYBODY. WHAT I UNDERSTAND IS WE DO HAVE TIME; BUT AS WE MOVE INTO, NOT THAT MUCH TIME, CLINICAL TRIALS ARE ALREADY HAPPENING, BUT AS WE START TO MOVE INTO EVEN MORE, IT'S OUR RESPONSIBILITY TO ESTABLISH GUIDELINES. I MEAN THERE ARE GUIDELINES THAT ARE ALREADY THERE, SO WE'RE NOT REINVENTING THE WHEEL, BUT TO LOOK AT THEM, MUCH LIKE WE DID WHEN WE DID THE OOCYTE DONATION, AND TO SEE, OKAY, THIS IS A NEW AREA OF SCIENCE. CAN WE ADD SOMETHING TO IT, CAN WE ADAPT, WHATEVER, CAN WE MAKE IT MORE SPECIFIC TO THE RESEARCH THAT WE'RE DOING IN THE CLINICAL TRIALS THAT WE'RE DOING?

AND I REMEMBER ONE OF THE SPEAKERS, I BELIEVE IT WAS YOU, SAY WE'RE THE GROUP THAT HAS THE POWER TO DO THIS. WE'RE THE GROUP THAT IS FUNDING THIS. WE HAVE THE RIGHT TO DO THIS. AND SO I THINK THAT'S OUR MISSION. AND I THINK ALL OF THE TOPICS THAT YOU LISTED ARE GOOD, AND WE MAY THINK OF OTHER

ONES. I THINK WE KIND OF ALREADY HAVE A SENSE OF CONSENSUS IN WANTING TO HAVE THIS MEETING THAT BUILDS CONSENSUS. I THINK, UNLESS I READ EVERYBODY WRONG, WE REALLY DO BELIEVE IN THE FULL DISSEMINATION OF INFORMATION. I THINK THAT'S A PRETTY EASY ONE. AND WE REALLY DO WANT THE PATIENTS TO UNDERSTAND FULLY, AND WE'RE GOING TO FIGURE OUT HOW, MUCH LIKE WE DID WITH OOCYTE DONATION, BETTER THAN THE USUAL CLINICAL TRIAL SITUATION.

AND FREE CARE IS SOMETHING THAT WE HAVE TO TALK ABOUT. I DIDN'T SENSE THERE WAS A CONSENSUS.

I REALLY FEEL, YOU KNOW, ALAN, THAT WE'LL MAYBE COME UP WITH OTHER THINGS, BUT WE HAVE THE OBLIGATION AND THE RESPONSIBILITY, THIS GROUP, TO RECOMMEND TO THE FULL BOARD OF THE ICOC WHAT WE THINK ARE THE BEST PRACTICES FOR CLINICAL TRIALS.

AND SINCE I CANNOT LET THIS GO, I WOULD LIKE ALSO A DISCUSSION OF SHAM SURGERY. I REALLY THINK THIS IS -- I HAVE TO SAY AS A PATIENT ADVOCATE, I THINK THIS WILL BE A BIG DEAL IF WE JUST KIND OF IGNORE THIS ISSUE AND THEN IT HAPPENS, AND I HAVE TO THINK THE PATIENT ADVOCACY COMMUNITY. SO WHETHER THAT'S A SEPARATE MEETING, WHETHER WE BRING EXPERTS TOGETHER, I WOULD LIKE TO ADD THAT AS WELL.

CHAIRMAN LO: SO WHY DON'T WE PUT THAT UP

AS NO. 5. AND SHERRY AND I TALKED AT ONE OF THE BREAKS, AND ONE WAY TO START THAT MIGHT BE TO ACTUALLY HAVE A PUBLIC MEETING ON SHAM SURGERY AND BRING IN PEOPLE WHO HAVE THOUGHT ABOUT IT, WRITTEN ABOUT IT, AND SOME SPECIFIC EXAMPLES.

MS. LANSING: DISCUSS ALTERNATIVES.

DR. TROUNSON: SO, SHERRY, IT'S PROBABLY EVEN A LITTLE BROADER THAN THAT BECAUSE, AS I UNDERSTAND, SOME OF THE MEMBERS OF OUR BOARD AND OTHERS WHO ARE ASSOCIATED WITH THIS, THERE'S A NEED FOR THE PATIENT'S VOICE TO BE HEARD, THE PATIENT ADVOCATE'S VOICE, PARTICULARLY AT FDA, BUT ALSO YOU KNOW IT IS HEARD HERE, BUT YOU KNOW THAT THEY HAVE A SET OF RIGHTS WHERE THEY FEEL THAT THEY SHOULDN'T NECESSARILY BE IGNORED IN THE PROCESS.

AND I THINK THIS IS A REALLY DIFFICULT AREA BECAUSE YOU'RE TRYING DESPERATELY TO MAKE SURE THAT WHATEVER THE TRIAL WORK IS IS WELL SOUNDED AND IT'S GOT SOME PROBABILITY OF BRINGING FORWARD A TREATMENT BENEFIT. BUT I'VE HEARD FROM SOME OF OUR PATIENT ADVOCATES THAT THEY FEEL THAT THEIR VOICE NEEDS TO BE HEARD IN THIS. SO I THINK THAT IS IN ADDITION TO.

MS. LANSING: I TOTALLY AGREE. I MEAN I THINK EVERY ONE OF THESE ISSUES, OBVIOUSLY WE WANT

PUBLIC INPUT, WE ALWAYS WELCOME PUBLIC INPUT, AND I THINK WE'RE IN SUCH A UNIQUE SITUATION BECAUSE THE FUNDING CAME FROM THE CITIZENS. DO YOU KNOW? THIS IS QUITE DIFFERENT, AND SO WE HAVE THE RIGHT AND RESPONSIBILITY TO RECOMMEND BEST PRACTICES FOR CLINICAL TRIALS JUST AS WE'VE DONE THROUGHOUT THE ENTIRE PROCESS. AND YES, I THINK WE WOULD GO THROUGH THE PROCESS THAT WE ALWAYS GO THROUGH WHERE WE WOULD HAVE PUBLIC SESSIONS AND WE WOULD ASK FOR PUBLIC INPUT. I THINK THAT'S VERY IMPORTANT.

MR. SHEEHY: I JUST MIGHT MAKE THE SHAM SURGERY A LITTLE BIT BIGGER TOPIC AND ABOUT PLACEBO CONTROLLED TRIALS.

MS. LANSING: THAT'S FINE.

DR. TAYLOR: I THINK THAT'S --

MR. SHEEHY: AND THAT'S PART OF IT.

DR. TAYLOR: IT'S A BROADER ISSUE.

MS. LANSING: THAT'S FINE.

CHAIRMAN LO: OTHER THOUGHTS, COMMENTS, REACTIONS? MARIE, PLEASE.

DR. CSETE: I'D LIKE TO FRAME, SHERRY, A LITTLE BIT DIFFERENTLY WHAT YOU SAID, THAT RATHER THAN US DEVELOPING AND ESTABLISHING GUIDELINES, THAT WE NEED TO SCRUTINIZE AND BECOME MUCH MORE FAMILIAR WITH THE THINGS THAT ARE ALREADY OUT THERE AND

IDENTIFY AREAS IN WHICH PERHAPS THINGS WOULD GO THROUGH AN IRB, THINGS WHICH WOULD GO THROUGH AN IND APPROVAL WHERE WE WOULD NOT BE COMFORTABLE. I THINK IT WOULD BE -- IT'S ALREADY -- YOU'RE ALREADY ESTABLISHING ANOTHER FULL-TIME JOB FOR US, WHICH IS A VERY IMPORTANT ONE, BUT I DON'T THINK WE WANT TO BE WRITING GUIDELINES. I THINK, RATHER, WE'D WANT TO BE HAVING AN ONGOING DIALOGUE WITH THE PEOPLE WHO HAVE THE ENFORCEMENT ABILITY IN ESTABLISHING GUIDELINES, ADVISING THEM.

AND RIGHT NOW THE STATE OF THE FIELD IS SUCH THAT I THINK I WOULD ENCOURAGE YOU, AS WE'RE DEVELOPING A CONSENSUS CONFERENCE FOR PRECLINICAL KINDS OF STUDIES, TO MAKE IT DISEASE SPECIFIC BECAUSE OTHERWISE WE'RE GOING TO GET -- ALL OF THE QUESTIONS THAT WERE RAISED HERE DO NOT HAVE RIGHT ANSWERS. AND I WILL GUARANTEE YOU THAT WHEN YOU GET PARKINSON'S CONSENTS THAT CAME UP SO MUCH, EXPERTS IN THE ROOM, THEY WILL NOT AGREE ON WHAT THE PRECLINICAL AND CLINICAL STANDARDS ARE ALONG THE WAY. BUT HEARING THE RANGE OF OPTIONS AND THE REASONS FOR PEOPLE LANDING ON THEM WITH GOOD, ETHICAL, AND SCIENTIFIC FRAMEWORKS IS IMPORTANT FOR US TO HEAR.

DR. TROUNSON: MAYBE NOT NECESSARILY

PARKINSON'S.

DR. CSETE: WHATEVER.

DR. TROUNSON: IF WE'RE INTO SPINAL REPAIR OF SPINAL INJURY, MAYBE THAT ONE.

DR. CSETE: MACULAR DEGENERATION.

DR. TROUNSON: SHOULD BE OR MACULAR DEGENERATION.

DR. CSETE: SOMETHING WE FUND.

DR. TROUNSON: THAT WE'RE VERY CLOSE. MAYBE THEY'RE THE KIND OF THINGS BECAUSE PARKINSON'S MAY STILL BE SOME TIME OFF, AND, YOU KNOW, STANDARDS MIGHT SHIFT AND STUDIES MIGHT MAKE IT CLEARER. SO, YOU KNOW, THE RELEVANCE, I THINK, FOR US IS TO GET AS CLOSE AS POSSIBLE TO WHAT WE MIGHT BE INVOLVED IN.

CHAIRMAN LO: I JUST WANTED TO SORT OF ASK MARIE A CLARIFYING QUESTION. SO YOUR CONCERNS ABOUT NOT ISSUING NEW GUIDELINES, IS THAT MAINLY ON QUESTION ONE, OR WOULD YOU SAY ALSO FOR TWO, THREE, AND FOUR, THAT YOU WOULD NOT WANT TO SEE THE SWG OR ICOC RECOMMEND NEW GUIDELINES OR EVEN REGULATION FOR OUR GRANTEES.

DR. CSETE: TIMELY DISSEMINATION OF FINDINGS WE DO TO THE BEST OF OUR ABILITY ALREADY, AND WE HAVE MECHANISMS IN PLACE FOR DOING THAT. WE

HAVEN'T COME TO CLINICAL TRIALS, SO WE CAN'T INCLUDE NEGATIVE RESULTS OF CLINICAL TRIALS YET. BUT WE'RE TRYING -- WE ARE WORKING WITH OUR INVESTIGATORS TO GET THE NEGATIVE RESULTS OF THAT PRECLINICAL WORK OUT THERE.

MR. SHESTACK: THERE'S A NEED TO GET THIS WORK OUT THERE, THE NEGATIVE RESULTS OUT THERE.

DR. CSETE: SO FIRST OF ALL, WE'RE JUST GETTING RESULTS FOR THE VERY FIRST TIME FROM SEED GRANTS, FOR EXAMPLE, AND COMPREHENSIVE GRANTS. AND WHEN WE SEE SOMETHING THAT IS NEGATIVE AND WE ASK THE INVESTIGATOR, ARE YOU GOING TO PUBLISH THIS, AND THEY SAY NO, OR WE DON'T THINK WE CAN GET IT PUBLISHED.

WE HAVE TALKED WITH DON ABOUT HAVING THESE KINDS OF STUDIES OUT ON OUR WEBSITE SO THAT PEOPLE CAN -- YOU HAVE TO WORK WITH THE INVESTIGATOR OBVIOUSLY TO DO THAT. AND I THINK THAT'S ABOUT THE BEST WE CAN DO WITH THE SCIENCE AT THIS POINT. IF IT CAN'T BE PUBLISHED IN A JOURNAL, WE CAN CERTAINLY PUBLISH IT --

MS. LANSING: THAT'S ALL OUR OBLIGATION -- I MEAN THAT IS PART OF PROP 71 --

DR. CSETE: ABSOLUTELY.

MS. LANSING: -- WAS THAT EVERYTHING WOULD

BE PUBLIC, AND THAT MEANS PUBLIC ON OUR WEBSITE. WE CAN'T ASK SOMEONE TO PUBLISH IT IN THE *NEW ENGLAND JOURNAL*.

DR. CSETE: RIGHT. SO IN TERMS OF THE CONSENSUS MEETING, I JUST THINK THAT, FIRST OF ALL, THERE'S A LOT OF THESE KINDS OF MEETINGS COMING ABOUT NOW. THE ISSCR DOCUMENT WAS TIMELY BECAUSE OF IT. IT HOPEFULLY WILL BE A DOCUMENT THAT'S IN EVOLUTION. IN THE GENERAL TERMS, I THINK IF WE DO THIS RELATIVELY SOON, WE WILL SPEND TWO DAYS HAVING THE SAME DISCUSSION THAT WE HAD HERE. WE'VE NOW RAISED THE GENERAL ISSUES AND MADE YOU ALL AWARE OF THE GENERAL ISSUES, THOUGH I WOULD REALLY ENCOURAGE PEOPLE TO GO BACK TO SOME OF THE DOCUMENTS THAT HAVE BEEN PRESENTED TO YOU, INCLUDING THE BELMONT REPORT AND THE CITY KIND OF TRAINING FOR IRB'S, ETC., SO THAT YOU KNOW WHAT IS ALREADY THERE BEFORE MAKING RECOMMENDATIONS ABOUT WHAT CIRM SHOULD DO IN ADDITION.

BUT I THINK WE WILL GET MUCH MORE MEAT OUT OF A STANDARDS MEETING IF WE GET EXPERTS TO TALK ABOUT A SPECIFIC PROBLEM BECAUSE THEN I THINK YOU WILL UNDERSTAND THAT THE NEXT LEVEL OF RESOLUTION IS THAT PEOPLE WILL ARGUE ABOUT WHAT THE BEST ANIMAL MODEL IS, PEOPLE WILL ARGUE ABOUT WHAT THE BEST

CLINICAL OUTCOME -- END POINT FOR ANALYSIS IS IN BOTH THE ANIMALS AND HUMAN SUBJECTS. AND, YOU KNOW, PERHAPS THERE WILL BE SOME CONSENSUS THAT COMES OUT OF THESE THINGS, BUT OFTEN CONSENSUS MEANS THIS IS A RANGE OF PRACTICE.

MS. LANSING: LET ME ASK YOU A QUESTION BECAUSE BERNIE ASKED A SPECIFIC QUESTION, AND I DON'T THINK THERE'S DISAGREEMENT, BUT MAYBE I'M MISUNDERSTANDING IT. NONE OF US ARE SUGGESTING THAT WE START FROM SCRATCH. I MEAN I DON'T THINK ANYONE IS SAYING THAT. WE'RE ALL SAYING THERE ARE EXISTING GUIDELINES. YOU KNOW THEM BETTER THAN WE DO. AND WE'RE ACTUALLY LOOKING TO YOU TO RESPOND TO THESE ISSUES. SO YOU'RE RESPONDING TO THE FIRST ONE BY SAYING IF IT'S NOT DISEASE SPECIFIC, IT'S TOO HARD.

DR. CSETE: NO. I DIDN'T SAY IT'S TOO HARD. WE'RE JUST NOT GOING TO MAKE PROGRESS. I THINK WE'LL GET MORE MEAT OUT OF SOMETHING SPECIFIC.

MS. LANSING: WHAT WE'RE ASKING YOU TO DO, I THINK, BERNIE, CORRECT ME IF I'M WRONG, THESE ARE THE ISSUES THAT CAME OUT OF THESE TWO DAYS. AND MAYBE THERE WILL BE SOMETHING ELSE. MAYBE WE'LL E-MAIL EACH OTHER AND THERE WILL BE SOMETHING ELSE. CAN YOU LOOK AT THESE ISSUES AND SAY HOW YOU WOULD SUGGEST THIS GROUP, WORKING WITH YOU, TACKLES THESE

ISSUES? THAT'S ALL WE'RE ASKING YOU TO DO, AND YOU MAY SAY JUST WHAT YOU SAID ABOUT THE FIRST ONE. UNLESS IT'S DISEASE SPECIFIC, YOU'RE NOT GOING TO GET CONSENSUS. WITH THE SECOND ONE, YOU'RE SAYING WE DO THAT ALREADY, AND THIS IS HOW WE DO IT.

SO IF YOU'RE IN AGREEMENT, WE CAN PUT THAT IN BEST PRACTICES, BUT IT'S ALREADY IN PROP 71. I CAN'T GO -- THE OTHER ONE, THAT'S SORT OF UP TO US TO SEE HOW WE CAN GET INFORMED CONSENT TO BE BETTER. AND FREE CARE IS A WHOLE THING THAT WE WOULD HAVE TO DO, AND SHAM SURGERY IS A WHOLE -- PLACEBO IS A WHOLE OTHER THING THAT WE WANT TO DISCUSS. THAT'S ALL.

CHAIRMAN LO: WHAT I'M SUGGESTING IS THAT IF THESE ARE ISSUES THAT SWG HAS IDENTIFIED AS BEING WORTH PURSUING, THAT GEOFF AND I AND SHERRY WORK TOGETHER TO KIND OF FLESH THESE OUT AND MAKE THEM MORE SPECIFIC AND THEN COME BACK AND WORK WITH MARIE AND ALAN AND OTHERS AT CIRM TO SAY WHAT'S NOT FEASIBLE, WHAT'S ALREADY BEING DONE. AND ON THINGS WHERE THERE IS A SORT OF A GAP OR OPPORTUNITY, JUST SORT OF IDENTIFY OPTIONS HOW TO PROCEED NEXT, AND THEN COME BACK TO THE SWG.

DR. CSETE: I JUST WANT TO MAKE A CAUTIONARY NOTE ABOUT NO. 3. THERE'S HUGE PATIENT

CONFIDENTIALITY ISSUES IN THERE, AND OUR ACCESS TO PATIENTS IS SOMETHING WE'D HAVE TO EXAMINE VERY CAREFULLY.

CHAIRMAN LO: WELL, WE WERE THINKING OF SOMETHING SIMILAR TO THE REQUIREMENT FOR OOCYTE DONATION WHERE WE'RE NOT GOING TO BE ASSESSING IT OURSELVES, BUT THERE NEEDS TO BE A PLAN IN THE PROTOCOL THAT THE INVESTIGATOR HAVE SOME WAY OF ASSESSING THE COMPREHENSION AND THAT THE LOCAL IRB HAS APPROVED THAT. SO AGAIN, IT'S A MODEST FIRST STEP, BUT IT DOES BREAK THE MOLD OF SAYING AS LONG AS YOU PUT IT IN THE CONSENT FORM, WE'RE OKAY.

DR. CSETE: RIGHT. SO, SHERRY, JUST SO YOU KNOW TOO, WE FULLY ANTICIPATED THAT AS THINGS MOVE TOWARDS CLINICAL TRIALS, JUST AS IN ANY OTHER SPONSORING AGENCY, THAT THE WHOLE IRB APPLICATION AND CONSENT FORMS AND ALL THAT WOULD BE PART OF WHAT GETS REVIEWED. AND SO THAT'S ALREADY ALSO PART.

DR. TROUNSON: BUT I THINK, BERNIE, THERE'S ALWAYS THE OPTION TO IMPROVE UPON WHAT WE'RE DOING. AND SO IT'S A MATTER OF UNDERSTANDING WHERE WE CURRENTLY ARE, BUT WHERE WE MAYBE SHOULD MOVE TO TO IMPROVE IT BECAUSE, YOU KNOW, WE ARE EXPECTED, I THINK THE WORLD IS LOOKING AT US FOR LEADERSHIP IN THESE AREAS. SO IT'S IMPORTANT THAT YOU KNOW THAT

YOUR MESSAGES GET TO US, AND WE CAN SEE WHERE WE LOGISTICALLY AND LEGALLY AND APPROPRIATELY CAN MOVE OUR WHOLE PROCESSES TO INCORPORATE THESE. AND THEN I THINK THAT BECOMES THE MOVING FRONT, AND IT WILL KEEP MOVING, IT'S A MOVING FRONT, AND I THINK IT'S THEN VERY WORTHWHILE TO HAVE YOUR INPUTS IN DOING THAT.

CHAIRMAN LO: AND AGAIN, I JUST WANT TO STRESS THAT THIS IS THE BEGINNING OF A PROCESS. AND WE MAY COME BACK AT THE NEXT MEETING AND SAY, WELL, NO, NO. 17 WON'T WORK. NO. 18 WE'RE DOING ALREADY. NO. 19 IS A BAD IDEA WHEN WE THOUGHT ABOUT IT MORE. SO WE'RE NOT SAYING WE DEFINITELY WANT TO PUSH IT. THESE ARE TOPICS THAT WE THINK BEAR MORE THOUGHT AND SORT OF INVESTIGATION.

JEFF.

MR. SHEEHY: I JUST THINK NOW THAT WE'RE GOING INTO CLINICAL TRIALS, THE DISSEMINATION OF NEGATIVE RESULTS, I DO THINK WE NEED TO REEXAMINE. HAVING BEEN ON THE IP TASK FORCE AND LOOKED AT SOME OF OUR REPORTING REQUIREMENTS, THEY REALLY TENDED TO FOCUS ON DISCLOSURE OF SUCCESS. AND WE WERE REALLY LOOKING AT PATENTS. WE WERE LOOKING ABOUT WHEN YOU FILE A PATENT, WHEN YOU PUBLISH. IN CLINICAL TRIALS WE MAY ONLY -- WE'RE ONLY GOING TO BE FUNDING ONE

PIECE OF IT. AND I REALLY THINK WE SHOULD BE VERY EMPHATIC ABOUT GETTING NEGATIVE TRIAL RESULTS RELEASED BROADLY, QUICKLY. AND THERE'S NO INCENTIVE FOR A COMPANY TO DO THAT. AND COMPANIES WILL BE THE ONES THAT ARE DOING CLINICAL TRIALS. I MEAN THEIR STOCK -- THEY'RE GOING TO WANT TO TIME IT SO THEY CAN CASH OUT THEIR STOCK. I'M NOT THAT CYNICAL. I TAKE THAT BACK.

BUT LET'S BE PERFECTLY HONEST. THERE'S A DIFFERENT MOTIVATION GOING ON, AND HAVING LISTENED TO THE DISCUSSION, I'M HORRIFIED BY THE THOUGHT THAT SOMEONE COULD BE, EVEN IF IT'S NOT A CIRM-FUNDED TRIAL, COULD BE ENROLLED IN A TRIAL IN A DIFFERENT SETTING THAT HAS ALL OF THESE DIFFERENT RISKS WHEN WE KNOW THAT THAT PARTICULAR APPROACH DIDN'T WORK AND THAT THE COMPANY IS SITTING ON THE DATA, FOR WHATEVER REASON, MAY BE MOTIVATING THEM NOT TO DO IT IMMEDIATELY. AND I THINK NOW THAT WE'RE COMING TO THIS PHASE, WE SHOULD REALLY LOOK AT WHAT KIND OF REGULATORY ACTION WE CAN TAKE.

DR. KIESSLING: I WOULD ACTUALLY REALLY LIKE TO SEE THIS GROUP PUT SOME PRESSURE ON THE MAJOR JOURNALS. THIS IS A RECURRING PROBLEM THAT YOU CAN'T -- THERE'S TWO KINDS OF THINGS YOU CAN'T GET PUBLISHED. YOU CAN'T GET THE REPEAT STUDY

PUBLISHED. NOBODY WANTS TO PUBLISH THE REPEAT AND CONFIRMATORY. AND NOBODY WANTS TO PUBLISH A NEGATIVE RESULT. BUT I THINK THAT A LETTER FROM THIS GROUP OR SOMEBODY BRINGING THIS UP TO LIKE THE *NEW ENGLAND JOURNAL* OR *JAMA* OR *CELL* OR ANY OF THE MAJOR JOURNALS THAT DON'T LIKE TO PUBLISH THESE THINGS, THAT THIS IS REALLY IMPORTANT PATIENT-RELATED INFORMATION.

DR. TROUNSON: AND, I THINK THIS IS CHANGING TO BE -- YOU KNOW, THE WORK WITH THE MAJOR JOURNALS, IT IS MUCH EASIER NOW TO GET THAT SECOND PAPER AND THIRD PAPER PUBLISHED IN THOSE TOP JOURNALS. SO IT IS A MATTER FOR US TO BE STERN AND ENCOURAGING ABOUT IT, AND IF WE'RE ON EDITORIAL BOARDS, TO DO THAT. AND I CERTAINLY AM. AND SO, YOU KNOW, I THINK NEGATIVE RESULTS, AS I SAID BEFORE, ARE JUST AS IMPORTANT, MAYBE EVEN MORE IMPORTANT THAN THE POSITIVE ONES BECAUSE IT MIGHT SAVE SOME PATIENTS GOING PLACES TO GET TREATMENT WHICH WILL BE REGRETTABLE, DANGEROUS, AND UNNECESSARY IF THEY HAD THAT FURTHER INFORMATION.

MR. SHESTACK: I JUST WANTED TO CONFIRM THIS. WE HAD A SITUATION IN AUTISM WHERE SOMEBODY DID A TREMENDOUS AMOUNT OF RESEARCH ON GENETICS OF, SAY, HEAVY METALS AND CLEARANCE OF HEAVY METALS.

AND THEY DIDN'T GET ANY RESULT -- THEY DIDN'T GET THE RESULTS THAT THE PEOPLE WHO PAID FOR THE STUDY WANTED. SO THEY JUST MOVED ON TO A DIFFERENT SET OF HEAVY METALS, AND PERHAPS IT MIGHT HAVE CHANGED A CERTAIN DEBATE SIGNIFICANTLY. WHO KNOWS?

BUT WHAT I WANTED TO ASK TO BE PUT ON THE SUGGESTION FOR THE WORKING GROUP IS MORE IS -- I DON'T EVEN KNOW THE RIGHT WORD -- MAYBE SORT OF PRAGMATICS, WHICH IS TO SAY WHAT CIRM CAN DO TO HELP PEOPLE IF FUNDS MEET THE STANDARDS THEY NEED TO MEET IN ORDER TO GO ON TO THE NEXT STAGE OF A TRIAL. IF, FOR INSTANCE, THE GOLD STANDARD IS THAT YOU CONDUCT YOUR INITIAL INVESTIGATION WITH TWO ANIMALS AND HAVE A REPLICATION SET, THAT'S TRUE. NOBODY WANTS TO PAY FOR THAT. NOBODY WANTS TO EVEN WRITE THE GRANT FOR THAT. THAT IS JUST A DRAG AND IT NEVER GETS DONE, BUT YOU NEED TO DO IT.

SO WHY WOULDN'T -- AND THAT IS THE GOLD STANDARD. SO WHY WOULDN'T CIRM, FOR INSTANCE, SET ASIDE A TRACK OR A FUND OR SOME KIND OF MECHANISM THAT COMMISSIONS IT AND JUST GETS IT DONE? YOU HAVE. WELL, THEN GREAT. AND IF THERE IS ANYTHING LIKE THAT THAT ARE SORT OF HAVING TO DO WITH BOTH STANDARDS AND THEN SOME PRAGMATIC THINGS THAT CIRM CAN DO TO HELP FUND THESE TO MEET THOSE STANDARDS,

THAT WOULD TRULY BE, I THINK, KEEPING IN MIND THE GOALS OF THE CITIZENS OF CALIFORNIA WHO WOULD LIKE TO GET THESE THINGS EITHER TO WORK OR NOT WORK FASTER.

DR. TROUNSON: WELL, I THINK THAT'S REALLY WHAT WE CALL TRANSLATION, JOHN. THAT'S OUR PERSPECTIVE OF IT, THAT, YOU KNOW, ACADEMIA DOESN'T LIKE DOING IT MUCH BECAUSE IT'S HARD TO GET SOME OF THAT STUFF PUBLISHED, AS YOU SAY. IT'S DULL, IT'S INTELLECTUALLY NOT NECESSARILY SO CHALLENGING. BUT THAT'S WHAT WE'RE SORT OF HARD CASING IN ON TO TRY AND SUPPORT THAT AT THE CURRENT TIME ACROSS A BROADER SPECTRUM AS WE THINK IS APPROPRIATE.

MR. SHESTACK: SO WHAT'S THE SPECIFIC PROGRAM THAT DOES IT?

DR. TROUNSON: IT'S THE EARLY TRANSLATIONAL STUDIES THAT DO THESE THINGS SPECIFICALLY. BUT ALSO THE DISEASE TEAMS WILL HAVE A COMPONENT OF THAT AS WELL.

MR. SHESTACK: SO THERE'S EXTRA FUNDING BUILT IN TO DO THIS MUCH LESS GLAMOROUS WORK?

DR. OLSON: THE PRECLINICAL DEVELOPMENT COMPONENT OF DISEASE TEAMS IS BASICALLY THE SAFETY AND TOXICOLOGY STUDIES, THE GLP PHARMACOLOGY STUDIES, THE STUDIES THAT AREN'T NECESSARILY THE

SEXY THINGS, BUT THINGS THAT YOU HAVE TO DO TO ESSENTIALLY FILE A REGULATORY APPLICATION. AND THEY'RE VERY IMPORTANT.

MR. SHESTACK: OKAY. THANK YOU.

CHAIRMAN LO: OKAY. SO WITH THAT, I WANT TO THANK ALL OF YOU FOR A VERY STIMULATING MEETING. AND THEN GEOFF WILL WORK WITH ALAN AND MARIE AND SHERRY AND I TO SORT OF DEVELOP THESE IDEAS FURTHER, AND WE'LL BE BACK TO YOU THROUGH E-MAIL AS WE SORT OF MOVE AHEAD. THANKS VERY MUCH.

(THE MEETING WAS THEN ADJOURNED AT 1:20 P.M.)

REPORTER'S CERTIFICATE

I, BETH C. DRAIN, A CERTIFIED SHORTHAND REPORTER IN AND FOR THE STATE OF CALIFORNIA, HEREBY CERTIFY THAT THE FOREGOING TRANSCRIPT OF THE PROCEEDINGS BEFORE THE SCIENTIFIC AND MEDICAL ACCOUNTABILITY STANDARDS WORKING GROUP TO THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE IN THE MATTER OF ITS REGULAR MEETING HELD AT THE LOCATION INDICATED BELOW

LUXE HOTEL
11461 W. SUNSET BOULEVARD
LOS ANGELES, CALIFORNIA
ON
FEBRUARY 17 AND 18, 2009

WAS HELD AS HEREIN APPEARS AND THAT THIS IS THE ORIGINAL TRANSCRIPT THEREOF AND THAT THE STATEMENTS THAT APPEAR IN THIS TRANSCRIPT WERE DIGITALLY RECORDED AND SUBSEQUENTLY TRANSCRIBED BY ME. I ALSO CERTIFY THAT THIS TRANSCRIPT IS A TRUE AND ACCURATE RECORD OF THE PROCEEDING.

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