IMWEL Engineering Research Center for Integrated Mechanobiology for Women's Health

IMWEL Ten-Page Response to Site Visit Reviews
NSF ERC: Integrated Mechanobiology for Women's Health

We appreciate the review panel's supportive comments. In Section A, we respond to **Significant Weaknesses (SW)** and some **Other Questions (OQ)** the SVT raised with clarifications. Where the **SW** prompted **Proposed Adjustments,** we address them in Section B**.** Responses follow verbatim review comments and questions. We are eager to continue refining IMWEL in response to this and future feedback.

1. SIGNIFICANT WEAKNESSES (SW)

SW: "There were inconsistencies in the definition of engineered system between the proposal and the vision articulated by the senior leadership during the Q+A session." – We apologize for the apparent inconsistency. The top-level of IMWEL's engineering system is a set of physiological systems testbeds, each representing a health challenge that uniquely or disproportionately affects women and has origins in biomechanics and mechanobiology. The Engineering System remains a constellation of technologies to maintain or restore the biomechanical form and function of our systems testbeds.

SW: "It was not clear how formative evaluation would be conducted on an ongoing basis at all participating institutions." – Evaluation leadership will meet quarterly with a liaison identified at each institution, both individually (with members of their respective institutions, as needed) to plan evaluation activities, and as a group, to facilitate cross-institution communication, coordination, and data-sharing. This evaluation liaison model has been effective in other large multisite, multicore evaluations in ensuring that efforts are efficient, adhere to overall program aims, and are tailored to institutional data needs, and that findings are used to inform decision making. The model is further described below.

SW: "...there were no metrics for success defined. There were limited specifics on how the outcomes of the evaluation exercises would influence the broader activities on the ERC." – Using a participatory approach, the evaluator and stakeholders will together define evaluation from the start, meet frequently to discuss needs and data, and collaboratively interpret findings and their implications. The evaluator's annual reporting will examine ways in which evaluation feedback has been used and acted upon and whether that action (or nonaction) had any impact on component functioning. Evaluation findings will be shared broadly across the ERC, such that all IMWEL personnel will have access to the data necessary to foster and influence success. As for specific metrics for success, the following table includes examples for each of our major goal areas.

Evaluation Area	Sample of Metrics
In assessing research advances by testbeds and research components:	• Number of innovations at basic research, pre-clinical, and clinical levels; • Number of publications and subsequent funding by researchers; and • Time to market.
To determine if the pipeline of researchers in the field of female reproductive bioengineering is expanding, we will measure:	• Number of middle school students taking STEEM courses in high school; • Number of high school students pursuing STEEM careers in college; • Number and demographics of REU students pursuing female reproductive bioengineering or a related field in graduate school; • Number and demographics of graduate students retained in the field of female reproductive bioengineering or a related field; • Reasons for pursuing/continuing or not pursuing/continuing the field of female reproductive bioengineering; and • Experiences with inclusion and equity while working in or pursuing education in the field of female reproductive bioengineering.
With regard to commercialization, we will assess:	• Number of devices supported in development towards proof of concept; • Number and commitments of businesses who are part of the ecosystem; • Number of devices translated into the ecosystem; • ROI of products translated into the ecosystem; and • Health impact from devices translated into the ecosystem.

OQ: "The evaluation plan as integrated into the workforce development plan was not well defined." – EWD evaluation will examine if strategies (from educational interventions in middle school through inclusive leadership and mentorship programs) are implemented as intended. It will also explore any

barriers and facilitators to these strategies; these might be internal (e.g., communication, organization) or external (e.g., IRB, school partnerships, leadership support); findings will be shared to facilitate change and promote best practice. In addition, the evaluation team will assess strategy outcomes and impact, meeting at least quarterly with the EWD component leads to discuss information needs, progress toward component goals, and findings. Data collection will be coordinated with EWD so that efforts are not duplicated. Evaluation of EWD strategies, such as educational interventions, REUs, RETs, equity and inclusion initiatives, and pipeline development, will rely on existing validated instruments when possible. These will be chosen in collaboration with EWD and may include Partnership in Education and Resilience [1], Undergraduate Research Student Self-Assessment [2], and CIMER Assessment Platform.

OQ: "It is likely that effective evaluation…may require resources well beyond the external evaluator. It is not clear…how either institutional assessment or other IMWEL participants will assist in the processes described." – To leverage evaluation, we are employing an institutional and component liaison model: A liaison will be identified at each institution and within each component, who will be an important member of the evaluation team. Liaisons, as a group, will meet quarterly with the evaluation lead to facilitate cross-institution and cross-component communication and data-sharing. The evaluation team will also meet with liaisons and other key members of their institution or component quarterly to understand data needs, examine barriers that affect IMWEL, and discuss findings from formative studies, resulting in data-driven.

SW: "A major weakness in the site visit was that the industry partners could not clearly articulate the vision of the Center. They were focused on some limited current partnerships without commitment for future investment or risk sharing." – We take responsibility for this miscommunication. Our current stakeholders represent trusted, existing partners, and we advised them to discuss existing collaborations. They are committed to enhancing the discovery of clinical needs, collaborating on tech development, expanding our partner connections, and improving our access to necessary resources, including additional funding (which will come from existing firms or new strategic partners) through industry membership. Upon launch, a robust industry relations effort will include a dedicated website, social media campaigns, and marketing materials to disseminate our vision. We will complement the Center broadcasts with regular insight-seeking surveys and polls to solicit their guidance. We will utilize our respective technology development and transfer offices to highlight technologies ready for licensing and our testbeds and lab-to-market accelerators as entry points for engagement and mutual learning. Securing and maintaining industry relations will be an ongoing effort throughout the life of the Center. GE Global Health expressed their interest in a partnership just after the proposal submission. We are currently also in discussions with Cook, Medtronic, Abbott, Becton Dickinson, Lioness, Dame, and Ceek Women's Health.

SW: "A notable weakness was that the Engineering Workforce Development plan does not consider industry needs or inputs." + OQ: The EWD plans would be improved if internship opportunities for undergraduate and graduate students were available, particularly with larger industry partners already established in the gynecological devices space." – Industry partners are part of a bi-directional knowledge transfer and communication system: we get insights into knowledge gaps and possible focuses; our partners get early knowledge of test results and new inventions. Faculty may use examples from our technology development and partner companies in teaching; our industry partners want opportunities to meet and recruit students at all levels, from undergraduates to postdoctoral fellows. Thus, while not explicitly mentioned in our EWD plans, industry internships are planned as part of our engagement with our company members. Summer internship opportunities for our students have proven to be a practical, effective approach to professional development and, at the same time, provide companies an ability to assess technical knowledge and cultural match.

SW: "The plan for women-centered design, innovation, entrepreneurship, and commercialization was exciting but much of this activity falls outside the control of the Center." + OQ: "It seems likely…IP developed…would need to be licensed out and…much of the technology development, capitalization, and commercialization effort would therefore happen outside…of IMWEL." + OQ: "The smaller companies may not have the resources to acquire technology that is not fully de-risked, and the Center itself does not have the resources to fund clinical trials that will likely be needed." – The Innovation Ecosystem's goal is to build self-sustaining university, industry, and community partnerships to catalyze the rapid development and commercialization of novel solutions to improve women's lives. IE's role is to promote, train, advise and prepare entrepreneurial teams for a runway toward commercialization, not fund or control them; hence much of the activity will indeed fall outside the control of the Center. We will catalyze innovation and entrepreneurship by developing innovative technologies and new concepts, inspiring students, postdocs, faculty, and outside entrepreneurs to engage in women's

health, and providing training, connections, seed funding, and help to network with external sources of funding to bring their ideas to reality. A typical pathway: a university's scientific or conceptual development is licensed by a startup, which in turn gains financial support from investors, and is eventually acquired by an enterprise with scale and distribution to affect the standard of care. IMWEL universities each have a proven track record of bringing technologies to market. By combining resources, we will build a critical mass of technical, financial, and regulatory expertise in this nascent MedTech field. IMWEL's commitment to women-centered design, encapsulated by the IE's mantra "nothing for us, without us" will permeate all four pillars. We believe IMWEL will prove an example for our universities, catalyze change through our IE ecosystem, and spread the impact as IMWEL's students, graduate students and postdocs permeate other universities, industry, and startups in the future.

OQ: "One weakness of the [IE] team appeared to be the heavy reliance on postdocs to develop technologies and potentially become new entrepreneurs. The postdoc mentoring plan was weak with respect to plans for developing the skills that these individuals would need…" – IMWEL's strategy is to create an Ecosystem of Innovation with multiple partners and alternative paths to commercialization. Our collective experience shows that venture-backable startups most often commercialize new and transformative innovations. These often depend on an engaged lead from the technical team, usually a graduating Ph.D. or postdoc willing to take a leave from their academic career. CU has successfully run over a dozen Lab-to-Market Accelerator Programs (L2M), which take aspiring entrepreneurs through a Lean LaunchPad/I-Corps inspired boot camp to learn customer discovery, marketing, and pitch-making; connect to mentors from venture capital, industry, and the startup community; find experienced business executives; and meet sources of angel and VC funding. We have run these Accelerators on behalf of multiple joint institutions, as we will for IMWEL. BioMedX, a Biomedical Engineering LTM has spurred 12 startups, 6 licenses to industry and attracted $80M in external capital.

OQ: "The strategy of focusing on smaller/startup-level companies for industry partnerships was perceived as a drawback…" – There is a perception that universities *prefer* to license technologies either to startups or to large companies. They typically explore both options, as will IMWEL. Some innovations may appeal to large companies (e.g., where scientific risk has been addressed and commercialization efforts would focus on clinical trials, scale-up, manufacturing, marketing, and sales). Others are better suited for startups (e.g., technologies that need de-risking to validate the underlying science prior to commercialization; or platform technologies best utilized across varied industries).

SW: "The site visit did not provide clarity on the potential implications of replacing consortium institution ECU with WashU. In particular, the broader impacts…due to respective locations." – WUSTL brings a deeper bench of research, clinical expertise, and resources for broader impacts than ECU. The SVT points out ECU offered a window on first-generation students, from small towns and rural areas. St. Louis is the only city in a broad geographic area composed primarily of small towns and rural areas. Approximately 8.5% of WUSTL's engineering undergraduates are first-generation students. WUSTL's *Deneb STARS* supports 350 students who are first-generation or from under-resourced socioeconomic backgrounds. *WashU Pledge* provides free undergraduate education to incoming, full-time students from Missouri and southern Illinois who are Pell Grant eligible or from families with annual incomes of <$75k. WUSTL also recently announced it was investing $1B in financial aid to adopt a need-blind undergraduate admissions policy. *WUSTL Summer Engineering Fellowship* supports research experiences for undergraduates from diverse backgrounds. The *Institute for School Partnership* partners with schools in the St. Louis community. WUSTL's 750 full-time clinical faculty staff the Barnes-Jewish Hospital, which sees 80,000 patients annually in its emergency department and is the fifth-busiest aeromedical service in the nation. Dr. Dineo Khabele, Chairman of the Dept of Obstetrics & Gynecology, noted recently: "as a Black woman…I am more motivated than ever to work for change…As obstetricians and gynecologists in St. Louis, we witness how Black women are dying prematurely and disproportionately from complications of pregnancy, women's cancers, and now, COVID-19" [3]. Lastly, we note IMWEL continues to work with ECU's Linda May, who studies exercise during pregnancy.

We address the following Significant Weaknesses below under Proposed Adjustments:

SW/PA: "A major concern for some of the reviewers was that Testbed 3 (cardiac and musculoskeletal physiology) was not synergistic with the women's health initiatives explored in Testbeds 1 & 2 and was not reflected in industry partnerships."

SW/PA: "The scientific and engineering vision for the ERC is threatened by the lack of one of the pioneering women's reproductive organ health bioengineering researchers in the role of PI."

SW/PA: "Some reviewers had reservations about curricular development within the K–12 systems and whether or not this is entirely appropriate or feasible. Evidence of engagement from partnership K–12 institutions may have helped reduce these reservations."
SW/PA: "Explanation of bioethical considerations were not integrated sufficiently in the proposed research plans."
SW/PA: "Concerns were also raised about the lack of risk assessment regarding the human subjects research plans and medico-legal exposure involving vulnerable populations."
SW/PA: "The community advisory board cannot provide independent feedback to the ERC under the structure currently defined."

2. PROPOSED ADJUSTMENTS

PERSONNEL, MANAGEMENT, & ORGANIZATION

SW/PA: "Explanation of bioethical considerations were not integrated sufficiently in the proposed research plans." + SW/PA: "Concerns were also raised about the lack of risk assessment regarding the human subjects research plans and medico-legal exposure involving vulnerable populations."
Unique bioethical challenges associated with pregnancy, fetal tissue, and vulnerable medical populations warrant a unified approach. We have devised a cross-institutional approach that provides a Center-specific coordination of local institutional IRBs, IACUCs, and bioethics experts including multisite agreements (such as a single IRB—sIRB—discussed below). This approach addresses bioethical challenges in the Center's Convergent Research and adds a bioethics training component to EWD. This training component is particularly crucial given the history of unquestionably unethical surgical experimentation on slaves in the 19th century in the development of modern OB/Gyn, and of Henrietta Lacks's cervical cancer cells taken without her informed consent in the 20th century.

Established bioethics researchers Jessica Mozersky (IMWEL Bioethics Council Chair) and Alison Antes (Co-Chair and Training Lead) from the Bioethics Research Center at WUSTL have joined IMWEL to direct the cross-institutional Bioethics Council. Mozersky and Antes have partnered with multidisciplinary teams to identify and conduct empirical research on bioethical issues that emerge during all phases of research from study design to dissemination of findings. Each institution will have a Council representative (Fig. 1). This council will focus on project-wide and interinstitutional bioethical concerns, as well as support the training component and act as a first point of reference for questions regarding ethical challenges encountered. The CARE (collective benefit, authority to control, responsibility and ethics) and FAIR (findable, accessible, interoperable and reusable) principles, originally developed for research with Indigenous populations but highly applicable for many other populations [4], will serve as the bioethical framework that guides IMWEL cross-institutional collaborations. This will inform how we address bioethical issues identified during the project.

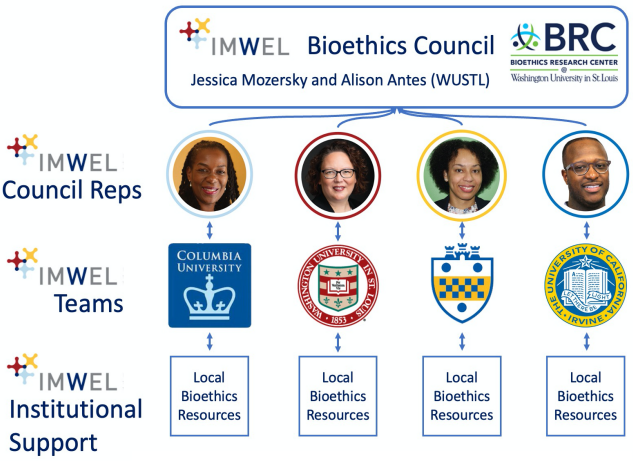

Fig. 1: Bioethics Council organizational chart.

Local institutional resources, including bioethics researchers at each Center site, will support the Center and issues identified by Council Representatives at each site will be collated and communicated to the Bioethics Council. The Council will also oversee a bioethics training component for all participants (investigators and trainees). Bioethics training will include practical knowledge and skills to foster responsible conduct of research including human subjects' protections, research protocol compliance, ethical and transparent data sharing, community-engaged research, and team science. Each institution is an NIH Clinical and Translational Science Award hub site. Individual institution IRBs will cover most research but if a broader (i.e., sIRB) framework is required, CU will lead.
OQ: IRB reliance/authorization agreements are also not in place and the team has not grappled yet with sIRB (single IRB) issues." – CU as the lead and responsible institution has experience with sIRB approaches and signed onto NCATS's new SMART IRB Reliance Agreement in 2016. CU provides IRB services to non-CU institutions or investigators for 152+ active studies. CU serves as the Central IRB for

40 studies, including those conducted by 12 member institutions of the Perinatal Research Consortium. Its robust Human Research Protection Program supports more than 7600 human subjects research studies, overseen by seven IRBs that also serve as Privacy Boards for HIPAA compliance. WUSTL as the lead on bioethics also has significant sIRB experience and will consult in cross-institutional issues.

SW/PA: "The scientific and engineering vision for the ERC is threatened by the lack of one of the pioneering women's reproductive organ health bioengineering researchers in the role of PI." – Following the SVT's and NSF's recommendation, we designate X. Edward Guo as Center Director (CD) and Kristin Myers as Lead PI. This change reflects the partnership IMWEL has crafted over the past four years, ever since the brainstorming workshop that catalyzed IMWEL, and reinforces the responsibilities described in our proposal. As PI, Myers will spearhead the research vision and mission, ensuring that IMWEL achieves and advances the goals of the convergent research. As an experienced manager familiar with the demands of multi-institutional centers, CD Guo will be responsible for overall management. Kam will remain Deputy Director, continuing to contribute his administrative experience with center management.

SW/PA: "The community advisory board cannot provide independent feedback to the ERC under the structure currently defined. This body would be more valuable if it were made up of and chaired by independent members who are not researchers funded by the ERC. It was not clear how the feedback from the community advisory group would be collected, provided to the leadership, and used to inform the activities of the ERC." – We agree independent members should chair and primarily compose the Community Impact Advisory Board (CIAB), including participants among health care providers, physical therapists, patient advocacy groups, public policy practitioners, members of university community engagement cores, and women's-health industry leaders. The CIAB Chair will interface directly with IMWEL's Executive Committee (EC) and provide a SWOT analysis annually to the EC and external evaluator. To reinforce our commitment to women-centered design, the EC, pillar leads, a chair of the bioethics team, and physician-scientist leads Moalli and Lowder will attend the CIAB meetings. Each meeting will also have a closed-door session for the independent stakeholders only.

New ERC CIAB partners Pregnancy After Loss Support (PALS), Push for Empowered Pregnancy, Hand to Hold, Sisters in Loss, and South Florida March of Dimes have agreed to participate; Every Mother Counts, The Tiny Miracles Foundation, Saul's Light, and NICU Parent Network have expressed interest.

OQ/PA: "The lack of inclusion of researchers or health services practitioners who work in exercise physiology, kinesiology, gait/motion analysis, physical therapy, or pelvic floor rehabilitation was a serious weakness." – IMWEL does include this community, with named team members Linda May (ECU) who studies exercise during pregnancy, Spencer Lake (WUSTL) researcher in Center of Regenerative Medicine, and Ellen Casey (HSS), physiatrist at Hospital for Special Surgery's Women's Sports Medicine Center. To bolster this effort, we have added experts Monica Daley (UCI Neuromechanics Lab) and Tracy Spitznagel (Physical Therapy, WUSTL).

CONVERGENT RESEARCH

SW/PA: "A major concern for some of the reviewers was that Testbed 3 (cardiac and musculoskeletal physiology) was not synergistic with the women's health initiatives explored in Testbeds 1 & 2 and was not reflected in industry partnerships." + "OQ/PA: "While part of the focus is on pelvic floor health, overall, this testbed appears to be tacked on to the proposal with indirect links to the first two testbeds and integrations to women's health. There is not much information regarding how the expertise offered in this testbed will fundamentally advance women's issues." – We may have confused the SVT about this important and integrated Testbed by calling it "Healthy Aging," which might have implied a focus on the aged. Therefore, we have renamed our Testbed "Healthy Living," reflecting its goals more accurately. As stated in the full proposal, the Healthy Living Testbed will develop strategies and technologies to maximize the effects of exercise to maintain and improve women's health during their entire life [5][6]. Pregnancy rigorously stresses the female reproductive system and other organ systems (e.g., cardiac output increases by 50%). Exercise benefits the whole body, particularly the cardiovascular and musculoskeletal systems, including those supporting the female reproductive system and the pelvic floor. The Preterm Birth Testbed focuses on diagnosing and preventing preterm birth and on maternal health. Obesity during pregnancy increases the preterm birth risks, as well as the child's proclivity for obesity. Evidence suggests exercise during pregnancy reduces preterm birth risk by 33% and reduces newborn childhood obesity by 53% [7]. Therefore, the Healthy Living Testbed synergistically connects with the Preterm Birth Testbed. Obesity and the lack of prenatal education in URM groups contribute significantly to maternal mortality and morbidity, especially in cardiovascular and metabolic complications, such as

diabetes, hypertension, and pre-eclampsia. While hypertension is somewhat less common in women younger than 65 than in men, some sex-specific forms of hypertension only affect women, including postmenopausal hypertension, oral contraceptive-induced hypertension, and pregnancy-related hypertension. The last has especially significant effects on both the mother and the baby's lifelong risk of cardiovascular disease. Thus, the Healthy Living Testbed provides a critical venue to address health disparities in URM groups.

The Healthy Living Testbed also directly connects with the Pelvic Floor Disorders Testbed as the exact role of exercise and physical activities on pelvic floor health is still poorly understood. Studies show aerobic and anaerobic exercise benefit women of all ages and high-impact exercises reduce the incidence of osteoporosis and fragility fractures; can delay the onset of hypertension and heart disease; and be an interventional strategy to manage pelvic floor disorders—yet, curiously, women athletes and military personnel who engage in high-impact activities such as running, volleyball, trampoline, and parachute jumping have higher rates of pelvic floor disorders. Numerous studies observed improvement in pelvic floor muscle contraction using various methods including biofeedback, ultrasound, insertables, or surface devices. None of these tools provide quantitative and accurate assessment of pelvic floor muscle function. We will address basic research and technology gaps in accurately assessing pelvic floor muscle contractions and rehabilitation in women. Tremendous potential also exists for mobile pelvic floor biofeedback apps that include wearable and accurate sensors for pelvic floor muscle contraction, integrated with pelvic floor muscle exercise intervention. Science poorly understands the molecular mechanisms induced by exercise that support systemic musculoskeletal and cardiovascular health in women. IMWEL will use a mechanomics approach to identify and isolate molecular factors involved in the pro-health of the cardiovascular and musculoskeletal systems, with a specific focus on pregnancy, delivery, the postpartum period as well as post-menopause. The engineering system can develop technologies to maintain or restore the biomechanical form and function of our cardiovascular and musculoskeletal system through exercise.

Convergent Research. This Testbed will drive research on tissue and organ mechanobiology (R2), experimental cellular and tissue mechanics (R1), multiscale theoretical mechanics (R3), and mechanomics (R4). We will first define the basic science of exercise on the female reproductive system, pelvic floor, and cardiovascular functions using appropriate rodent models. IMWEL will utilize interventions such as treadmill, squatting, and jumping to measure their impact on the biomechanics of female reproductive system (uterus, cervix, vagina, pubococcygeus and iliococcygeus muscles, and the structural properties of the vagina–supportive tissue complex) in both pregnant and nonpregnant animals. IMWEL will collect tissues from the cardiovascular system (e.g., ventricle, aorta) and skeletal system (e.g., femur, tibia, spine). Finally, IMWEL will measure proteomics and genomics to identify mechanomics factors induced by exercise through blood and serum samples. We are especially interested in the effects of mode and intensity of exercise. In jumping exercises, we will look for clues in fatigue and injuries in pelvic floor muscles while maximizing skeletal bone benefit of exercise.

Enabling Technology. Various techniques including ultrasound and surface electromyography sensors have been incorporated in biofeedback to improve the efficacy of exercise on pelvic floor muscle contraction and function, but no tools exist to quantify pelvic floor muscle contraction in patients in real time. For example, pelvic floor muscle fatigue has been implicated in pelvic floor disorders; however, no technology can assess this in vivo. In the Technology Testbeds, we will focus on innovation for (1) multiscale and patient-specific, image-based computational models to provide accurate predictions of muscle force and physiology in patients T1, and (2) new multichannel, wireless, and wearable surface or intravaginal devices for measuring pelvic floor muscle contractions and feedback for both basic science and clinical applications (T3). A combination of functional MRI imaging and ultrasound can create multiscale computational models for pelvic floor muscle contraction predictions.

Healthy Living Testbed. Based on Convergent Research and Enabling Technology, IMWEL will conduct human subject studies. Briefly, a randomized controlled trial will measure and model musculoskeletal and cardiovascular responses, and the mechanomics of a prescribed exercise intervention. The Center will study premenopausal, current pregnant, and peri-menopausal women in an exercise regime of Aerobic and Resistance Exercises. The Center will also study nonpregnant women separately where they will be assigned to Aerobic or High-Impact Exercise. Inertial measurement systems that integrate multiple axes, accelerometers, gyroscopes, and other sensors will obtain musculoskeletal metrics; cardiovascular metrics will include heart rate, blood pressure, and echo-doppler derived measures of uterine blood flow in pregnant people. Importantly, we will assess our technology development in wearable or wireless devices and image-based multiscale modeling of pelvic floor muscle function

assessments. Through an sIRB, IMWEL will acquire blood samples for mechanomics studies to identify and isolate molecular factors associated with healthy cardiovascular and musculoskeletal biomechanical function. We will develop novel functional measures of cardiovascular and neuromuscular health alongside collecting established indicators of locomotor health and mobility throughout life, including preferred walking speed, gait asymmetry, and variability in step length and cadence. The proposed exercise intervention, which abides by the guidelines of the professional medical societies, builds on previous studies with positive findings conducted by Center consultant, Dr. May (ECU), an exercise physiologist with expertise in exercise training pregnant and postpartum women. As PI of an R01 funded exercise intervention with pregnancy and postpartum women, Dr. May will provide guidance and training to Center sites conducting the exercise intervention portions for this NSF study. At CU, Dr. Casey of the Hospital for Special Surgery, a physiatrist with experience in exercise studies in pregnant women will oversee clinical exercise studies with input from Dr. Liu from the University of Pennsylvania, a pregnancy bone expert. At WUSTL, physical therapist Spitznagle, an expert in both exercise in pregnant women and pelvic floor rehabilitation, will oversee studies in partnership with Dr. Lowder, the Chief of Female Pelvic Medicine and Reconstructive Surgery. At UCI, Dr. Daley, an expert in biomechanics of locomotion and sensorimotor control and Director of the UCI Human Performance lab will support the testbed.

Milestones. In five years, IMWEL will develop prototypes of wearable devices and mobile apps and associated algorithms for monitoring outcomes of exercise in cardiovascular and musculoskeletal systems. Building upon our expertise in developing sensors and inverse algorithms for measuring potentials and contractions from the heart and uterus from wearable sensors, we will design integrated wearable and wireless devices that are placed on abdominal or perineal surface and intravaginally to monitor pelvic floor muscle contractions and provide biofeedback in real time for pelvic floor muscle training and while exercising during pregnancy and postpartum. This device work will benefit from IMWEL industry partners (e.g., Materna Health and Renovia). Animal studies will test the plausibility of using MRI image-based computational modeling and ultrasound for modeling and measuring pelvic floor (specifically the pubocaudalis in the rodent) muscle contraction. By year 10, tested and validated technologies and devices will be primed for startups and licensing.

OQ: R1 – Experimental, Cellular & Tissue Mechanics – "In the context of the testbeds, the first project will examine hydrogel properties to mimic implantation conditions and measure trophoblast migration. The PIs note that the work will enable an understanding of mechanobiology – but it's not clear how. Nor is it clear how or if the mechanics of the system relates to third-trimester complications." – The full proposal stated: "a significant challenge in pregnancy research arises in that placenta-related complications in the third trimester of gestation are rooted in developmental issues that occur in the first trimester." It is known that trophoblast invasion is a combination of cell mechanics, kinematics, chemotaxis, and durotaxis and thus intrinsically mechanobiology. Insufficient trophoblast invasion in the first trimester is associated with preeclampsia and fetal growth restriction arising in the late second or early third trimester. These conditions are leading causes of preterm birth and as such early invasion of trophoblast leads to successful term pregnancy.

OQ: R1 – Experimental, Cellular & Tissue Mechanics – "A rodent model was proposed for understanding tissue biomechanics in the reproductive system. This needs stronger justification based on the anatomical differences between rodents and humans." – We addressed this extensively in the SVT daily site-visit responses. Additionally, similar criticisms were made of the rabbit model for knee ligament injury research in the 1980s, yet that model allowed for a major paradigm shift in the way we currently treat those injuries. Our group understands the opportunities and limitations of animal models well; our team has published a review article related to the biomechanics of the pelvic floor in animal models [8]. Marianna Alperin, a former trainee of Abramowitch and Moalli, developed a successful NIH-funded research career using the rodent and rabbit to answer questions relevant to pelvic floor disorders [9]. This work and ours show that anatomical differences present either advantages or disadvantages depending on the specific research question of interest. The rat has been a successful model for studying the consequences of a simulated birth injury in terms of continence and pelvic organ support. This model has also been critical in identifying the roles of superficial muscles for sexual function.

OQ: R1 – Experimental, Cellular & Tissue Mechanics – "There is not a clear research plan or milestones for the research." – The Measure-Model-Make paradigm showcased the following during the site visit: (1) in years 1–2, measurement of cell and tissue biomechanical properties, including but not limited to uterus and cervix, fetal membrane and placenta, pelvic floor and perineum, cell migration and trophoblast invasion, and hormone effects on cardiovascular and musculoskeletal tissues; in years 3–5, iterating with

R3 and T1 efforts (theoretical and computational modeling) to establish further needs for experimental data; and in years 6–10, using obtained data and models to support T2 and T3 development (research and clinically deployable devices). The research needs for tissue properties include the use of established measurement techniques along with the development of new testing and data analysis modalities, such as soft tissue fracture mechanics experiments.

OQ: R2 – Tissue & Organ Mechanobiology – "the flip in focus to cardiovascular and bone biomechanics and mechanobiology is not well justified and distracts from specific mechanical responses within the reproductive tract." – The specific physiologies and questions that R2 will examine are driven by the goal of understanding how mechanical cues coordinate with hormones and other soluble factors to drive the function of cells within reproductive tissues. The Healthy Living Testbed will now integrate cardiovascular and musculoskeletal systems with the reproductive targets of the other Testbeds and aims to examine how exercise and injury impact the mechanical factors present within these tissues.

OQ: R2 – Tissue & Organ Mechanobiology – "the use of human tissue from a vulnerable patient population was perceived as a risk to success. The feasibility of procuring critically important reproductive cells/tissues for this research (e.g., cervix, uterine wall/lining), was not established." – Please see response above concerning the new Bioethics Council, and site-visit response detailing current ongoing IRB-approved sample collection. In addition, IMWEL will take advantage of large biobank repositories housed by the NIH NICHD Maternal Fetal Medicine Units Network (CU and Pitt participate) and WUSTL's Women and Infants Health Specimen Consortium.

OQ: R4 – Mechanomics: "The research plan is largely appropriate but lacks defined milestones and necessary details." – The mechanomics milestones support the testbed timelines. Years 1–2 focus on establishing workflows, profiling the physiologies of target tissues, and identifying mechanobiology signatures from mechanically manipulated cells. Years 3–5 use this knowledge to guide *ex vivo* models and develop collection systems. Years 5–10 fully deploy these tools across testbed systems.

OQ: Tech Testbed Big Data and Bioinformatics – "Lack of model interpretability … is a huge risk." – CU is a leader in the shift in machine learning from mere statistical association to understandable models, providing mechanistic insight and commercial / regulatory interpretability. IMWEL will use several approaches. First, analysis of perturbations such as clinical interventions pinpoints the outcomes of drugs or treatments. Second, the temporal nature of data, e.g., from pregnancy visits or fitness activity trackers, informs us regarding causes vs. effects. Third, leveraging previously identified causal connections facilitates unearthing of new relationships between variables.

OQ: Preterm Birth Testbed – "it is unclear whether mechanical factors are significant contributors and that mechanical solutions will significantly alter clinical outcomes." – Preterm birth is classified into five categories (fetal, maternal, placental, associated with initiation of parturition, and birth-related [10]). In each of the first four, a substantial number of preterm births are associated with obvious mechanical factors, as was shown in the site visit slide decks: maternal (trauma, uterine rupture, pre-eclampsia); fetal (polyhydramnios, fetal growth restriction, multiple gestations); placental (placental abruption); birth-related (cervical shortening, cervical dilatation, preterm premature rupture of membranes). Thus, although not all preterm births have an obvious mechanical factor, a large fraction do (PPROM 3% of pregnancies and 40% of all preterm births; pre-eclampsia 10% of all pregnancies; fetal growth restriction 10–15% of pregnancies; cervix-associated preterm birth 5% of pregnancies). For a range of preterm birth etiologies, which can overlap, mechanical interventions would significantly affect clinical outcomes if appropriate diagnosis, intervention, and prevention strategies were available.

OQ: Pelvic Floor Disorders Testbed – "it is not clear what the technological developments will be within the time frame." – Please refer to site-visit slides. Briefly, Years 1–2: Enable currently developed solutions (e.g., our mesh alternative) to achieve commercialization via our innovation ecosystem. Our prototype mesh alternative is now undergoing evaluation in animal models and has been submitted for a provisional patent. Years 3–5: Develop the first-ever solution for treatment of a levator ani muscle injury detectable via imaging, viz. our composite scaffold technology for enthesis repair. This technology has been utilized in orthopedic applications and will require modification for the application proposed here. Years 5–10: develop the first-ever subject-specific and population-informed solution for preventing pelvic floor disorders through an imaging and computational workflow based on fundamental science gained in this ERC.

ENGINEERING WORKFORCE DEVELOPMENT

SW/PA: "Some reviewers had reservations about curricular development within the K–12 systems and whether or not this is entirely appropriate or feasible. Evidence of engagement from partnership K–12 institutions may have helped reduce these reservations." – We are glad that the extensive experience working with K–12 instruction as more fully outlined in the Day Two responses to SVT questions helped alleviate concerns. We will secure the appropriate IRB and FERPA compliances, child assent and parental consent, and ensure activities are age-appropriate and approved by parents, school boards and school leadership. Given the mindfulness developing curriculum takes, it is important to recognize that the curriculum—a formal educational set of materials—will be the result of research that is carefully conceived and executed over the life of IMWEL. Thus, our responses will focus on the research needed to reach that end goal. We address appropriateness and feasibility of the research separately below.

Appropriateness of research: First, PI Myers and Co-PI Oyen have a book in process that MIT Press will market as a school-based physics textbook to introduce high school students to principles of engineering and women's health. This book will be a cornerstone of the research needed to develop the curriculum. Second, concerns about the appropriateness of the research are an empirical question incorporated in the initial stages of our research plan. How do diverse types of content and aspects of biomechanical engineering maximize student engagement and learning while minimizing parental concerns about appropriateness of the content? Do aspects of the educational materials trigger concerns more than others? Does geographic variation of the research sites matter? In answering these questions, we will heavily engage our community and student boards.

The proposed five years of rigorous research needed to develop a curriculum includes: (1) a needs assessment that surveys students and teachers to identify psychological (e.g., embarrassment communicating about women's bodies), pedagogical (e.g., lack of curricula) and institutional barriers (e.g., few educators with STEM training) that face students and teachers as well as anticipate areas of opportunity (e.g., interest in health at younger ages); (2) developing and testing a series of randomized double-blind longitudinal interventions designed to increase engagement, interest and academic performance in STEM courses; and (3) identifying best-practice strategies for the interventions. We design initial needs assessment surveys to better understand how to conceptualize and measure the appropriateness of the intervention materials. Moreover, we can design laboratory research to empirically understand what parents and teachers perceive is appropriate. Third, we have built informal relationships with superintendents, principals, and teachers. We often share parts of the Oyen and Meyers textbook, and the responses we have received thus far are ones of excitement about the potential to offer a new lens of conceptualizing engineering to students. One school principal of a local NYC public school said, "Our school has a group of highly active 8th grade girls who started a menstrual awareness group and want to raise awareness among boys and girls here at school. Is there a place for that in your curriculum?" Each school district will bring its own challenges, but the content of the experiments can be as pedestrian as teaching about differences in sex chromosomes to the biomechanics of pregnancy. We are confident that we will be able to design curricula that will be novel, usable, scalable, and acceptable.

Feasibility of research: We agree with the assessment that formal partnerships with K–12 institutions are critical. In pre-pandemic years securing letters of partnerships would have been standard operating procedure. During the pandemic when school leaders have been consumed with massive operational challenges, we opted to reach out informally through our institutional networks. In our view, the best way to develop long-term partnerships is to understand the situation on-the-ground at the schools. We did conduct a feasibility analysis before submitting the preproposal that allayed our concerns and that of the original committee. This analysis included: (1) focus groups with principals ranging from 1–4 participants per group; (2) focus groups with parents of middle school children; (3) hiring a naïve middle school science teacher and leveraging his general science knowledge to develop curriculum content ideas; (4) strategizing with the CU IRB about feasibility. We will leverage our institutional relationships, e.g., Dr. Downing, head of EWD for this Center, is a faculty director of OC–STEM, a partnership between UCI and the Orange County School district. We have been assured that our research can be launched as part of their program.

OQ: "At the college level, the plans for educational interventions and senior design projects could be made more impactful by making them more inclusive across disciplinary boundaries." – IMWEL draws on many departments–for example, besides Biomedical Engineering, IMWEL faculty represent Mechanical Engineering and Material Science (Myers, Bayly, Lake), Electrical Engineering (Hendon), and Computer Science (Pe'er). IMWEL welcomes students from all engineering departments.

OQ: "The postdoc mentoring plans did not address industry-specific needs or career preparation." – IMWEL's emphasis on advancing the interdisciplinary nature of its research will advantage postdoctoral scholars as industry values employees who are familiar with the vocabulary, conceptual frameworks, and research approaches of disciplines beyond their own. Similarly, postdocs will receive annual training in Team Science, which translates well to industry. IMWEL will also leverage institutional Offices of Postdoctoral Affairs for soft skills such as interviewing in industry versus academia as well as offering entrepreneurial training in the IE plan. Finally, postdocs will benefit from the new Bioethics training program outlined above, which is relevant for all career paths.

DIVERSITY & CULTURE OF INCLUSION

OQ/PA: "The team does not describe a plan to overcome the barriers to K–12 intervention…The plan for developing inclusive language for public-facing content and patient recruitment materials was not specified." – A critical part of any program of research is to include a robust contingency plan. While our team has discussed and articulated a plan to overcome barriers in K–12 interventions, we did not have space to present these. In our experience, school-based research's chief hurdle is usually sample size. We do not anticipate this being a barrier to IMWEL's projects, given the depth and breadth of initiatives of each university. However, we will send letters of inquiry to every single school district in each of our four states to increase opportunities for more schools to participate in this research effort and increase sample size. In addition, we can overcome any sample size barrier by partnering with the Growth Mindset Network (GMN) to conduct this research online. Dr. Purdie-Greenaway, DCI co-lead, is a member of this network. GMN has access to over 20 partner school districts with over 10,000 students and the infrastructure to conduct school-based research online.

Regarding inclusive language for public-facing content and patient recruitment materials, we proposed early in IMWEL's development an internal glossary to create alignment and understanding among this community. This glossary aims to raise awareness, guide learning, and support the use of culturally sensitive terms and phrases. Where appropriate, we center the voices and perspectives of those who are often marginalized or stereotyped. This glossary will also explain the origins for problematic terms and phrases and offer suitable alternatives; we anticipate finalizing the complete glossary by launch. However, we realize we need a public-facing glossary. Developing this will include meeting with the Community Impact Advisory Board to discuss content and define terms and appropriate usage. We will consult our IE ecosystem colleagues to develop the appropriate format (e.g., infographic, standard glossary) and delivery mechanism (e.g., digital, paper, app). We can develop this public-facing glossary within 24 months.

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