ADVARRA
advancing better research

December 12, 2019

The Honorable Elizabeth Warren
United States Senate
Washington, DC 20510

The Honorable Bernard Sanders
United States Senate
Washington, DC 20510

The Honorable Sherrod Brown
United States Senate
Washington, DC 20510

Re: Response to Letter Requesting Information on Advarra IRB

Dear Senator Warren, Senator Sanders, and Senator Brown:

I write on behalf of Advarra in response to your letter dated November 15, 2019, which requests information about our Institutional Review Board (IRB). Advarra believes that your letter raises important considerations that every IRB across the country must take into account in providing robust ethics review services.

We are happy to share with you additional information highlighting the commitment to excellence demonstrated by Advarra in our role as an IRB performing ethics reviews to protect human subjects in research studies. We are proud of our pivotal role in safeguarding the rights and welfare of the participants in research studies that help to develop new lifesaving and life-extending treatments and cures, benefiting patients and our health care system throughout the United States and Canada.

Advarra IRB conducts high-quality review of research, which is guided by a talented team well-versed in the regulatory and ethical standards governing human subjects research, as well as a robust internal compliance program, and written policies and procedures. IRB Members and leadership are integrally involved in ongoing discussions about how best to overcome new and evolving challenges in human research through participation and leadership in national conferences and events.

Leadership

Our commitment to excellence begins with the quality of our staff and IRB members. Our compliance and regulatory affairs functions are led by Advarra's Chief Compliance Officer and Institutional Official, Michele Russell-Einhorn. Ms. Russell-Einhorn is a national leader in human subjects protections and research ethics. Her experience includes more than ten years of leadership at

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the federal agencies charged with overseeing federally-funded research: as the Conflicts of Interest Attorney for the National Institutes of Health (NIH), and as the Director of Regulatory Affairs for the Office for Human Research Protections (OHRP) and its predecessor office, the Office for Protection from Research Risks (OPRR). Ms. Russell-Einhorn also served for 11 years as Senior Director of the Office for Human Research Studies at the Dana-Farber Cancer Institute, a leading, nonprofit National Cancer Institute-designated comprehensive cancer center that conducts pioneering cancer research.

Ms. Russell-Einhorn's current service to and role in the broader research community extend beyond her work at Advarra. Since 2014, Ms. Russell-Einhorn has served as co-chair of a subcommittee of the U.S. Department of Health and Human Services Secretary's Advisory Committee on Human Research Protections (SACHRP). Specifically, Ms. Russell-Einhorn co-chairs the SACHRP sub-committee on 45 C.F.R. Part 46, Subpart A (the federal regulations commonly referred to as the "Common Rule"), a committee comprising many of the most recognized researchers and professionals across the entire academic and industry research community in the United States.

Additionally, Advarra's Director of Regulatory Affairs is an attorney and formerly the Assistant Dean for Human Subject Protections at Johns Hopkins University and continues to be involved in advancing the research community's collective efforts. The Executive Chair of Advarra's IRB is also an attorney, who served at the Dana-Farber Cancer Institute and the Dana-Farber/Harvard Cancer Center for 11 years. In addition, several of Advarra's IRB Chairs hail from leading academic institutions and human research protection programs around the country.

Compliance and Quality Program

Ms. Russell-Einhorn leads a regulatory leadership team that oversees Advarra's commitment to the highest standards through an active compliance, quality auditing and monitoring program also supported by a robust Quality Assurance & Compliance team. Advarra's Quality Assurance & Compliance team is charged with auditing IRB activities to ensure consistency and compliance with federal requirements and with Advarra's own policies and procedures. The team systematically evaluates IRB review determinations, meeting minutes, and training records. Another critical component of our structure is the Quality Control team, the group responsible for conducting routine reviews of documents, including protocol and informed consent forms reviewed and approved by the Advarra IRB, prior to their release to the research team. This function serves as a double-check of our IRB's compliance with all applicable regulations, policies and procedures.

These functions ensure Advarra has a robust infrastructure and technology platform through which we can easily access information to monitor compliance and identify opportunities for improvement to our policies and practices. When the Quality Assurance & Compliance team identifies an opportunity for improvement, the regulatory leadership team works to address the issue through the appropriate means (*e.g.*, through changes to policies or processes, convening a process improvement focus group, or providing continuing education to IRB members and staff).

Policies and Procedures

Advarra's standards are anchored in our policies and procedures, which help ensure that IRB review is carried out in accordance with the criteria set forth in Food and Drug Administration (FDA) regulations at 21 C.F.R. § 56.111 and in the Common Rule at 45 C.F.R. § 46.111. In addition, for

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research that is not subject to FDA regulations or human subjects research regulations (the Common Rule), Advarra voluntarily applies the pre-2018 Common Rule requirements so that all research reviewed by Advarra follows clear, prescriptive criteria. Advarra has also established guidance documents, exhaustive checklists, and other resources for our IRB members that help ensure all required elements of human subjects protection are considered and applied. As an example, Advarra's policies require the Advarra IRB to evaluate whether a new research proposal being submitted to the Advarra IRB has been previously disapproved by another IRB. If a research proposal has been disapproved elsewhere, the Advarra IRB must specifically review and evaluate the rationale for the disapproval. In such situations, the Advarra IRB must actively consider any information about the disapproval as part of its evaluation of whether a proposed research project should be approved.

Advarra policies and procedures require IRB members and support staff to receive ongoing training, including new *ad hoc* trainings as requirements are revised, new federal guidance becomes available, or internal opportunities for improvement are identified through, for example, Advarra's quality assurance processes. Our polices require that we review our policies, procedures, and guidance documents periodically to capture insights gleaned through our quality assurance process and to incorporate evolving regulations and important issues being discussed amongst the national research ethics community.

Expertise and Independence of IRB Members

A significant strength of Advarra is the size of our IRB and the breadth of expertise amongst our IRB members. Federal regulations require that a convened IRB meeting consist of a quorum of a minimum of five members with at least one member with no affiliation with the institution (21 C.F.R § 56.107(d) and 45 C.F.R 46.107(C)). Advarra's pool of more than 140 IRB members across the United States and Canada far exceeds the federal regulatory requirements with approximately 82% of Advarra IRB members not otherwise affiliated with Advarra in any capacity. The balance are full-time IRB members who are qualified and trained to serve in this role as Advarra employees. Each IRB meeting meets the regulatory requirements for composition of an IRB including the presence of a non-scientific member at each meeting. It is the practice at Advarra to have unaffiliated members at each meeting as well, although this is not a federal requirement. Our scientific IRB members' expertise ranges across dozens of therapeutic areas, specialties, and disciplines. Advarra is also fortunate to have a diverse array of professions represented by Advarra's non-scientific IRB members, including clergy members, patient advocates, attorneys, and people who have survived life-threatening illnesses or diseases.

Importantly, the Advarra IRB will not make any final decisions on a research protocol unless and until adequate expertise for review has been secured and used. Advarra is most often able to leverage the deep experience and quality of our 140 board members in assembling an IRB panel with the appropriate subject matter expertise for a given research project; however, should we believe that additional expertise would benefit a particular research protocol, we also engage outside consultants to serve as members and bring additional insight to the IRB.

Advarra's policies and longstanding practice ensure that only IRB members can approve research proposals and sign off on other IRB decisions. Administrative staff, including myself and other members of the corporate executive leadership team, fully understand, appreciate, and respect that we do not have the authority to approve research and must not seek to influence the IRB's decision-making. Advarra policies further require all IRB members and any consultant subject matter

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experts who participate in the IRB review process to disclose all financial potential conflicts of interest and to recuse themselves from participation in the review of any project for which they do have a conflict of interest. Our policies make clear that no IRB member or consultant can participate in the review of any research for which they, or their immediate family, have a conflicting interest. Ms. Russell-Einhorn's experience with respect to this specific issue, including her seven years of service as the Conflicts of Interest Attorney at the NIH, is invaluable in this regard.

IRB Approvals of Research Projects, Including Studies in which Participants are Charged for Participation

The vast majority of research proposals reviewed by the Advarra IRB are approved only after the imposition of conditions (*e.g.*, significant modifications to the research protocol or informed consent document) that the IRB panel has deemed necessary to ensure compliance with the criteria for IRB review set forth under 21 C.F.R. § 56.111 and 45 C.F.R. § 46.111. During our latest routine assessment conducted internally as part of our enterprise risk controls, we analyzed approvals by Advarra IRB over a period of several months, and found that the majority of studies reviewed by the Advarra IRB imposed additional conditions to be met before IRB approval could be granted. As the Institutional Official for Advarra, Ms. Russell-Einhorn also retains the authority and the right, in accordance with the 21 C.F.R. § 56.112 and 45 C.F.R. § 46.112, to disapprove research approved by an Advarra IRB panel or send a protocol back to the IRB for further review. However, the reverse is not true, and she may not approve research that has been disapproved or not yet reviewed and approved by an Advarra IRB panel.

One of the issues described in your letter relates to research in which subjects must pay to participate (so-called "pay to play studies"). Advarra IRB follows FDA regulations and guidance on charging for investigational products to ensure that any such charges are appropriate, equitable, and clearly disclosed to research participants. Advarra has thought carefully about this issue, and recognizes the serious and complicated ethical considerations involved in determining whether these types of studies may be approved under applicable regulatory and ethical standards. In fact, our expertise, rigor, and leading thinking in this area are captured in an August 6, 2019 *STAT News* article, which you cite in your letter to us. The *STAT News* article actually begins with a quote from Ms. Russell-Einhorn, who explained that in each recent research proposal reviewed by the Advarra IRB involving this type of research, there were "serious concerns about how ethical it was to charge people to participate in the research – and whether it was absolutely necessary." The article also shares Advarra's perspective regarding the scope of this issue. These types of research proposals are still relatively rare and represent only a very small fraction of the thousands of protocols the Advarra IRB reviews annually. As indicated in the article, Advarra has indeed reviewed only a very small number of research proposals involving this type of research, in which subjects must pay in order to participate. The Advarra IRB has disapproved some of these studies, and deferred others pending additional information from study sponsors. For each study that has been approved, the IRB required the study sponsor to make significant revisions to the original study proposal as well as materials provided to the prospective human subject participants before the study could be approved.

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External Checks

The quality of our compliance program and our defining commitment to ethics are also demonstrated by external audits and our voluntary accreditation and assurance. Advarra is routinely audited by the FDA through the Bioresearch Monitoring Program. The last FDA audit occurred in July 2018 and resulted in no findings. Advarra is also fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). Accreditation is not mandatory, and although it is a voluntary process, Advarra firmly believes that committing our resources to achieve accreditation is key to ensuring the highest ethical standards in the review of human subjects research. Finally, Advarra has voluntarily obtained and maintains a Federalwide Assurance (FWA) from the federal Office for Human Research Protections (OHRP). Through the assurance, Advarra has voluntarily committed to compliance with the standards imposed under 45 C.F.R. Part 46, *Protection of Human Subjects*.

* * *

On behalf of the entire senior leadership team at Advarra, I thank you very much for your attention to the protection of human subjects participating in research. Our high standards for quality, accreditation, and regulatory compliance and the independence of our IRB members' decisions are fundamental to protecting human subjects, meeting the ongoing expectations of the research community and therefore maintaining the integrity of our entire enterprise. In short, we would not be able to sustain our business responsibly and effectively if we did not continuously adhere to the highest standards of ethics, independence, and regulatory compliance.

Advarra looks forward to continuing to help advance human subjects protections through active participation in leading external organizations (including SACHRP, SMART IRB, AAHRPP, PRIM&R and others) and a continued commitment to excellence in our own processes and procedures that support Advarra IRB reviews.

As this response contains confidential business information, we respectfully request confidential treatment to the fullest extent possible for this letter. We further request that you (1) refuse to grant third-party requests for access to the information contained herein; (2) notify Advarra (through written correspondence addressed to the Chief Executive Officer), by undersigned counsel, of any requests by any person, agency or entity to review, copy or otherwise obtain the information contained herein; and (3) provide Advarra with an opportunity to substantiate its claims of confidentiality before any such information may be released. If you have any questions, please do not hesitate to contact me at 410-884-2900 or via email at Pat.Donnelly@advarra.com.

Sincerely,

Patrick K. Donnelly
Chief Executive Officer

cc: Mark Barnes, Ropes & Gray LLP

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April [8], 2020

The Honorable Elizabeth Warren
United States Senate
Washington, DC, 20510

Re: Response to Request for Additional Information on Advarra IRB

Dear Senator Warren:

I write on behalf of Advarra in response to your staff's request for further information about our Institutional Review Board (IRB), following receipt of our letter dated December 12, 2019. We are happy to share with you additional information on Advarra's role as an IRB providing robust ethics review services.

Advarra IRB undertakes careful, high-quality review of research pursuant to procedures as further detailed herein, and is guided by a team that is experienced in the regulatory and ethical landscape governing human subject research.

Our team has demonstrated a commitment to excellence in safeguarding the rights and welfare of the participants in research studies that help deliver new lifesaving and life-extending treatments and cures that benefit patients and our health care system throughout the United States and Canada. We believe adherence to the highest standards of ethics, independence and regulatory compliance are integral to our business.

* * *

Review Process

Each year Advarra receives a distinct number of new protocols, site reviews, amendments and other protocol-related events for IRB review. There is also ongoing continuing review of protocols and sites reviewed in prior years, and this includes IRB review of amendments, continuing reviews, and reports from researchers and sites of their "unanticipated problems" and protocol deviations. IRB approvals typically may be identified as: (1) approvals, (2) approvals with modifications (this includes any type of modification regardless of the number of modifications), (3) deferrals and (4) disapprovals. IRB approvals with modifications must, from a regulatory perspective, be specific and concrete in the stated requirements. IRB deferrals are appropriate when the protocol requires substantive modifications – for example, if the IRB requests an explanation or justification of some major feature of a protocol.

Every submission to Advarra is carefully checked to ensure that all of our detailed questions are answered and that all relevant documents have been submitted. Many of the questions have been developed to be responsive to questions that typically arise at IRB review. In addition, there is a pre-review of the informed consent forms which necessarily results in questions back to protocol submitters. Finally, there are reviews by the IRB Chair and the primary reviewer during which pre-board-review

questions are identified and provided to the investigator/submitter for response. Thus, any protocol that is outright approved, conditionally approved or deferred or disapproved, has – prior to the IRB decision – advanced through several levels of review and, as needed, response. The number of protocols and approvals by Advarra is confidential business information, but generally speaking a small percentage of those proposals undergoing a full IRB review receives an outright approval at first IRB review; 80% are approved with required modifications; and a small number are deferred or disapproved. Deferrals and disapprovals are low in number because before any proposal reaches full board review, it has already been subject to significant analysis by the Advarra staff, the IRB Chair and the primary reviewer, and researchers have already made significant improvements in the submission, due to their early dialogue with Advarra. This situation is the result of the typically multiple back and forth reviews and responses that take place prior to the full IRB review, as described above.

Serious adverse events are reported to the sponsor but are not typically reported to the IRB unless they rise to the level of an "unanticipated problem" involving risks to subjects or others. The FDA guidance specifically states that SAEs are not to be reported to the IRB unless they rise to the level of an "unanticipated problem": Investigators are required to report promptly "to the IRB… all unanticipated problems involving risks to human subjects or others," including adverse events that should be considered unanticipated problems (§§ 56.108(b)(1), 312.53(c)(1)(vii), and 312.66)." https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adverse-event-reporting-irbs-improving-human-subject-protection. In 2019, Advarra received from sites and researchers approximately 500 reports of "unanticipated problems" that they have encountered in ongoing studies. As required by regulation and policy, the Advarra IRB analyzed those reports to understand potential risks to subjects and others.

Advarra reviews each protocol on its own merit regardless of the sponsor. Records are maintained by the title of the protocol and whether it is a drug, device, pediatric or other specific types of protocol.

Pay-to-Participate Trials

Pay-to-participate studies are relatively new, although the FDA has historically allowed companies to charge for investigational medical devices used in clinical trials. FDA guidance states that these charges should not exceed the amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device. In some cases, FDA will also authorize charging for investigational drugs used in clinical trials, provided specific requirements are met. In each of these cases, the potential costs to subjects must be included in the informed consent form. We assume that Senator Warren's query is focused on the pay-to-participate studies that have attracted recent media attention, such as the "young blood" plan in Florida to charge seniors as much as $285,000 to enroll in a trial to receive young-blood transfusions to delay aging – a trial with which Advarra was not involved. We note that this issue is of continuing concern to the research community. In response to this new trend in clinical trials, the FDA asked the HHS Secretary's Advisory Committee on Human Research Protections (SACHRP) to draft a recommendation on how the research community should evaluate these trials. Additionally, the National Institutes of Health also asked SACHRP to consider whether the NIH patient guidance resources adequately address the scenario in which patients are being asked to pay. To the best of our information, Advarra has reviewed, in total, only nine studies that meet this criterion of

"pay to participate." Of that number, four studies were disapproved; three were withdrawn or tabled permanently due to concerns expressed during the Advarra IRB review; and two were approved.

The following are some of the issues raised by the IRB in its review of some of these studies:

1. The Board had significant ethical concerns due to the lack of a strong scientific rational for the study combined with the high financial cost of participation for potential participants whose advanced age could make them vulnerable to the claims of promised benefit.
2. The Board had concerns with the overall scientific validity of the study.
3. The Board determined that the study would not ensure equitable selection of subjects and had concerns about whether the cost to participate could be substantiated.
4. The Board determined that, overall, there was insufficient scientific support for the protocol and because of this, the risks of participation significantly outweighed the potential benefits.
5. The Board expressed concern about charging subjects out-of-pocket for an unapproved stem cell intervention.
6. The Board expressed a need for a summary of the clinical trials conducted with the product to date, as well as a summary of available safety and effectiveness data, so that the Board can better assess the study's rationale, justification, and risk-benefit profile.

Conflict of Interest Policies

Advarra has robust policies and safeguards in place to manage real or perceived Conflict of Interest among Board Members, both affiliated and unaffiliated. Advarra's Conflict of Interest policies have been reviewed and affirmed by its accrediting body, AAHRPP. Board members, alternates, and consultants to the IRB must sign an attestation that they will disclose any conflicts of interest and manage the conflict per Advarra's written policies. All staff, including affiliated board members, must read, agree to, and acknowledge the IRB Policy Manual and Employee Handbook. Board members with conflicts of interest are not permitted to participate in the review or discussion of any item in which there is a conflict. Prior to the start of *every* Board meeting, the Chairperson queries the attending members soliciting disclosure of conflicts of interest for *any* item being presented on the agenda for discussion. Advarra's approach to managing and preventing board member conflicts of interest is consistent with the approach used by most academic IRBs in the U.S. Excerpts from the current Advarra Employee Handbook and the IRB Policy Manual that apply to IRB members are provided below.

Some recent situations in which personal conflict of interest concerns resulted in recusal of IRB members include:

1. An Advarra IRB member had a license agreement with a company that submits protocols to Advarra. The IRB member was not allowed to participate in the review of any protocols submitted by that company and was required to disclose the interest prior to the meeting; the recusal was recorded in the minutes per policy.

2. An Advarra IRB member was an investigator on a protocol submitted to Advarra. The IRB member was not allowed to participate in the review and discussion of that protocol.

3. An Advarra IRB member had conducted consulting activities for a CRO client for Advarra which had a protocol under review at the meeting. The member was not allowed to participate in the discussion and review of that protocol. The recusal was recorded in the meeting minutes per policy.

4. Per IRB Policy manual, external consultants retained for specific protocols are required to sign a Conflict of Interest Disclosure Statement on a per project basis. A consult report was requested from an expert in the field under study for a specific protocol. The consultant disclosed a professional financial relationship with the Sponsor of the study. The Board sought a consult from another, non-conflicted expert.

Percentage of IRB members with financial ties to pharmaceutical or medical device industry:

Advarra has a robust policy regarding actual or apparent conflicts of interest relating to the review of any research under its jurisdiction and again the policies have been reviewed and affirmed by the voluntary accreditation organization, AAHRPP. Advarra board members affirmatively agree to disclose any actual or apparent COI prior to a review and to not participate in any matter in which the member, spouse or dependent children have an actual or apparent conflict of interest; this approach is common among the majority of institutional review boards across the U.S.

Excerpts from the Advarra Employee Handbook and IRB Policy Manual Relating to Conflicts of Interest

1. Excerpt from Advarra Employee Handbook regarding Conflicts of Interest:

"A company's reputation for integrity is its most valuable asset and is directly related to the conduct of its officers and other employees. Therefore, employees must never use their positions with Advarra or any of its clients for private gain, to advance personal interests, or to obtain favors or benefits for themselves, members of their families, or any other individuals, corporations, or business entities.

Advarra adheres to the highest legal and ethical standards applicable in our business. The company's business is conducted in strict observance of both the letter and spirit of all applicable laws, and the integrity of each employee is of utmost importance.

Employees of Advarra shall conduct their personal affairs such that their duties and responsibilities to the company are not jeopardized and/or legal questions do not arise with respect to their association or work with Advarra."

2. Excerpt from Advarra IRB Policy Manual regarding Board Member Conflict of Interest:

2.0 IRB Member Conflicts of Interest (COI)

2.8.1 The IRB reviews submitted research with objectivity and in a manner that allows each IRB member, alternate, or consultant, to exercise independent judgment.

2.8.2 Conflicts of interest are conditions where the potential for a secondary gain, or a personal relationship, may preclude impartial or objective determinations in judgments related to the review of research. They could include, but are not limited to, relationships with individuals (financial or non-financial), agencies (government or non-government), hospitals, institutions and/or organizations such as pharmaceutical or biotechnology companies or device manufacturers and their contractors and vendors. Conflicts of interest could also include involvement in development of products (pharmaceutical, biotechnology, or device).

2.8.3 No IRB member, alternate or consultant can participate in the review of any research for which they, or their immediate family have a conflicting interest other than to provide information to the IRB. The immediate family of an IRB member, alternate or consultant is inclusive of spouse and each dependent child.

2.8.4 The IRB recognizes that conflicts of interest can arise from an IRB member, alternate, or consultant's relationship with the IRB as well as from relationships with other organizations involved in the research community.

2.8.5 All IRB members and consultants to the IRB are required to openly and promptly recuse themselves from participation in the review of any project for which they have a conflict of interest.

2.8.6 Members recused from review due to a conflict of interest are not counted toward quorum for the review of that project. In addition, the meeting minutes reflect recusal of that member or alternate for reasons of conflict of interest.

2.8.7 Additionally, the IRB recognizes that within its organization there are specific organizational roles (positions) that, because of their very nature, may create an appearance of conflict of interest. As such, the IRB may prohibit individuals with these roles from participating as members on the IRB.

2.8.8 Any individual providing consultation services which directly relate to a research project being reviewed by the IRB recuses him/herself from participation in review of the project, except to provide information to the IRB.

2.8.9 At the beginning of each IRB meeting, attendees are formally reminded of their obligation to disclose whether they have any conflict of interest. This reminder is in the meeting agenda and recorded in the meeting minutes.

2.8.10 If a member, alternate or consultant has a conflict of interest, he/she informs the IRB, recuses themselves, and leaves the meeting during the review of that project, except to provide information as requested by the IRB. It is not necessary for the IRB member or alternate to reveal to the IRB the nature of the conflict of interest.

2.8.11 IRB members are required to sign a Conflict of Interest Disclosure Statement at the time of initial appointment and are required to update their Disclosure Statements on an ongoing basis if and when applicable. Consultants sign a Conflict of Interest Disclosure

Statement on a per project basis.

2.8.12 The following interests and/or conditions signal conflicts of interest for IRB members, and consultants that require recusal from the IRB meeting during review of the project (except to provide information as requested by the IRB):

- Direct ownership in the company sponsoring the research, the CRO (if applicable) involved in the research, or the site conducting the research.
- Majority ownership or position of general partner, officer, director, or controlling shareholder of a client organization/sponsor.
- A proprietary interest in the test article.
- A proprietary interest in the outcome of the research project.
- Service as a PI or Sub-I on the protocol at a site overseen by the IRB or another IRB.
- Any financial conflict of interest (i.e., ownership interest, stock options, or other financial interest related to the research).
- No compensation related to the research.
- Any personal, professional, and/or financial involvement with the institution, product, sponsor, PI or subject which compromises objective evaluation of the research in the opinion of the IRB member.
- A personal determination that objectivity is compromised.

2.8.13 In the event that an IRB member or alternate cannot determine if he/she has a conflict of interest, he/she may consult with the IO or the IO's designee. In the rare instance that the IO, or the IO's designee and the member or alternate is unable to reach a determination, the member or alternate is presumed to be conflicted and is recused from the IRB meeting during review of the project, except to provide information to the IRB.

2.8.14 The following interests and/or conditions do NOT signal conflicts of interest for IRB members, and consultants that would require recusal from the IRB meeting during review of a project:

- Income from the authorship of academic or scholarly works. Income from seminars, lectures, or teaching engagements sponsored by public or non-profit entities.
- Income from service on advisory committees or review panels for public or non-profit entities.
- Equity managed by an unrelated, unbiased third party (e.g. invested in a mutual fund, including sector mutual funds).

* * *

On behalf of the entire senior leadership team at Advarra, I thank you for your continued attention to the protection of human subjects participating in research. We hold ourselves to the highest standards for quality, accreditation, and regulatory compliance in order to protect human subjects, meet the ongoing expectations of the research community, and therefore maintain the integrity of our entire business. Advarra looks forward to continuing to help advance human subjects protections through active participation in leading external organizations (including SACHRP, SMART IRB, and others) and a continued commitment to excellence in our own processes and procedures that support Advarra IRB review.

Because this response contains confidential business information, we respectfully request confidential treatment to the fullest extent possible for this letter. We further request that you (1) refuse to grant third-party requests for access to the information contained herein; (2) notify Advarra (through written correspondence addressed to the Chief Executive Officer), by undersigned counsel, of any requests by any person, agency or entity to review, copy or otherwise obtain the information contained herein; and (3) provide Advarra with an opportunity to substantiate its claims of confidentiality before any such information may be released. If you have any questions, please do not hesitate to contact me at 443-283-1529 or via email at Scott.Uebele@advarra.com.

Sincerely,

Scott E. Uebele
Chief Executive Officer

cc: Mark Barnes, Ropes & Gray LLP