CLINICAL RESEARCH AND SCIENTIFIC INTELLIGENCE – A WHITE PAPER

Envision HEALTHCARE

CENTER FOR QUALITY AND PATIENT SAFETY

AHRQ Certified Patient Safety Organization

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The human condition has advanced over time from a variety of activities, none more important than the contributions from medical research. New discoveries are acquired through actions and activities, which allow us to assimilate unknown information and merge it with pre-existing knowledge.

Questioning is the most important form of human thought and communication. The generation of knowledge fails in the absence of inquiry. Envision Healthcare is not only deeply committed to delivering the best care available today but is also faithful to the examination of the unknown. This monograph, created by a team of outstanding professionals, offers this treatise and set of tools to facilitate our ongoing quest to enhance clinical research.

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Two thousand five hundred and eighty years ago, the first documented human experiment was designed and published. Specifically, King Nebuchadnezzar of Babylon ordered that all of his people eat a diet of meat and wine. Daniel, a captured Israelite, refused for religious reasons and asked his guard to "test your servants for ten days: give us nothing but vegetables to eat and water to drink. Then compare our appearance with that of the young men who eat the royal food."[i] Two hundred and sixty-five years ago, the first controlled trial was conducted aboard the British Naval ship the HMS Salisbury.[ii] After 8 weeks at sea, Scurvy ripped through the crew making many prostrate before dying. On May 20, 1747 the ship's Scottish surgeon, James Lind, took 12 dying sailors and paired them in groups of two. Each pair received the same rations but were additionally given either "cider, diluted sulfuric acid, vinegar, sea water, two oranges and a lemon, or a purgative mixture."[iii] "The moft fudden and vifible good effects were perceived from the ufe of oranges and lemons," Lind wrote in 1757.[iv] Though controversy exists as to whether Lind's account was accurate, or even if his trial had ever been performed, the idea that variables need to be controlled for is critical to proper research.

In 1811, the first definition of a "placebo" would be published in Hooper's Medical Dictionary, and roughly, 50 years later, Dr. Austin Flint would compare a "dummy remedy" to an active treatment in patients with rheumatism.[v] Over the next century, the importance of hypothesis statements, masking, randomization, trial size, and defining proper outcome variables would further strengthen our ability to distinguish between an intervention's lack of effect, harmful effect, and benefit.

Today, the National Institutes of Health, which was formed in 1887, classifies clinical trials into five broad categories including Prevention, Diagnostic, Screening, Treatment, and Quality of Life. Trials within these categories are then classified by five phases: Phase 0. Exploring if and how a new drug may work; Phase 1. Safety, side effect, and dose range; Phase 2. Does the treatment work? Phase 3. Clinical trials: Is it better than what we currently have? Phase 4. Post approval long-term studies to determine population response differences and long-term side effects.[vi]

As the largest multi-specialty provider of physician services touching over 35 million souls annually, Envision Physician Services acts on its moral, ethical, and professional responsibility to assure that the care we provide to our patients is evidence-based and that we contribute to the evidence base for all patients, worldwide. To this end, Envision Healthcare's Division of Clinical Research and Scientific Intelligence is committed to the objective, ethical, and responsible conduct of research. EVPS is proud to be a founding member of the Southeast Florida Chapter of the Association of Clinical Research Professionals (ACRP) and we humbly take our position within the great history of clinical research by contributing well over 150 trials in a variety of clinical specialties. Our commitment to healthcare through clinical trial initiation, participation, and publication is our way of giving back to the global community.

Finally, we recognize that without patients who are willing to participate in clinical trials, there would be no trials or treatments. Envision Healthcare recognizes the courage of these individuals and is grateful to them for their engagement with us, for their trust in us, and for their support of our mission to enhance the care of our patients, their families, and communities nationwide.

WHY CARE ABOUT CLINICAL RESEARCH?

Clinicians sometimes have a distanced attitude towards research. The reasons for this are many: conducting research is difficult; it is only for those who are statistically minded; it means having NIH or equivalent funding; finally, it does not pertain to them, as research is separate from patient care. The notion that research is separate and without impact on patient care could not be more erroneous. Convincing clinicians that research is the cornerstone for advancing excellence in patient care often means putting it in a clinical context, so let us illustrate this with a few examples:

Example 1:

You are evaluating a patient with an acute ankle injury. Do you recognize the following questions?

- *Unable to bear weight immediately and in emergency department (E.D)?*
- *Tender on the lateral malleolar tip or posterior aspect of the lateral malleolus?*
- *Tender on the medial malleolar tip or posterior aspect of the medial malleolus?*

Most practicing emergency medicine clinicians will recognize these as the questions used for the Ottawa ankle rule. [i] This was a prospective survey administered in two stages: derivation and refinement of the original rules (first stage) and validation of the refined rules (second stage). The cohort consisted of a convenience sample of adults with acute ankle injuries: 1,032 of 1,130 eligible patients in the first stage and 453 of 530 eligible patients in the second stage. While these research method details may seem not useful to daily clinical practice, the results derived from this study certainly are.

Example 2:

What do the following physical exam findings represent?

- *No posterior midline cervical-spine tenderness*
- *No evidence of intoxication*
- *A normal level of alertness*
- *No focal neurologic deficit*
- *No painful distracting injuries*

The above represents the NEXUS low-risk criteria, which state that if a patent has all of the above, then they do not require cervical spine radiography.[ii] This prospective observational study was conducted across 21 centers in the U.S. The study population consisted of 34,069 patients evaluated by imaging of the cervical spine after blunt trauma. Of these, 2.4 percent had radiographically documented cervical-spine injury. These results yielded an overall sensitivity of 99 percent, a specificity of 12.9 percent and a

negative predictive value of 99.8 percent. Again, while conducting such a study may not appeal to everyone, the results from such investigations do affect everyday patient care.

Example 3:

- *A 45-year-old male presents to the E.D. with chest pain of 2.5-hour duration, radiating to the left arm, associated with diaphoresis, relieved by sublingual nitroglycerin in the ambulance and rated 5/10. Family history is unknown. What blood test will you order?*

The troponin story:[iii]

- 855 patients with symptoms of acute myocardial ischemia within 12 hours of onset had serum troponin T, creatine kinase-MB (CK-MB) and electrocardiogram (ECG) done and analyzed in blinded fashion. Logistic regression was used to assess the usefulness of baseline levels of troponin T and CK-MB versus ECG findings (ST-segment elevation, ST-segment depression, T-wave inversion or the presence of confounding factors that impair the detection of ischemia). On admission, 289 of 801 patients with baseline serum samples had elevated troponin T. Mortality within 30 days was significantly higher in these patients than in patients with lower levels of troponin T (11.8 percent versus 3.9 percent, $P < 0.001$). Troponin T levels remained significantly predictive of 30-day mortality in a model that contained ECG categories and CK-MB levels (chi-square = 9.2, $P = 0.027$). The authors of the study concluded that cardiac troponin T level is a powerful, independent risk marker in patients who present with acute myocardial infarction.
- Today, most clinicians routinely use this serum marker, perhaps not thinking about its origins from a research study.

So, why care about clinical research?

Clinical research is the way in which we can scientifically study patient outcomes and thus deliver evidence-based care. Our clinical practice is our laboratory — where we are continually gathering, classifying and analyzing data.[iv] While basic science and animal studies can provide important clues to the underlying pathophysiology of many human ailments, some nuances of human disease are not translatable from these models. Referred to as "the youngest science" by Lewis Thomas, the wonders of modern medicine are a direct result of medical research. Being involved in research offers the clinician the satisfaction of discovery and the honor of contributing to the care of those whom they will never know.

"The real voyage of discovery consists not in seeking new landscapes, but in having new eyes." -Marcel Proust

INTRODUCTION

Envision Healthcare (EVHC) touches more than 35 million patients on an annual basis. Given that magnitude, managing clinical research to ensure compliance and Good Clinical Practice (GCP) is like aiming at a moving target. The Clinical Research Department within EVHC (EVCR) was established in early 2000, at a point when research opportunities were rare. Since then, healthcare and science have greatly advanced, there are numerous opportunities to pursue research, and clinical trials are oftentimes a patient's only option. EVCR's efforts remain focused on staying abreast of drug and device development, keeping providers engaged along with maintaining GCP, educating and supporting providers in maintaining regulatory compliance and providing patients with access to investigational treatment.

Clinical research is governed by federal law focused on protecting patients. Noncompliance presents significant risks to patients, clinicians and organizations. The Federal Policy for the Protection of Human Subjects was published in 1991. *45 CFR part 46 Subpart A*, also known as the Federal Policy or the "Common Rule" … outlines the basic provisions for Institutional Review Boards, Informed Consent, Federal wide Assurances for the Protection of Human Subjects and Assurances of Compliance.[v] In 2017, the Department of Health and Human Services (HHS) and the Food and Drug Administration (FDA) revised their existing human subjects' regulations, making them as compatible as possible under their respective statutory authorities. Information on this and related federal laws and regulations is available at https://www.hhs.gov/ohrp/regulations-and-policy.

HUMAN SUBJECTS' SAFETY IN RESEARCH

> "*… avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm … Learning what will, in fact, benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks*."[vi]

Human subjects (study participants) are essential to clinical research. Numerous federal laws and regulations, as well as professional ethical responsibilities, command the protection of study participants throughout the research process and beyond. The Belmont Report,[vii] written in 1979, remains a primary source of guidance for the conduct of completing safe and principled clinical research and identifies respect, justice and beneficence as basic ethical considerations.

Respect. Study participants enter into research voluntarily and with adequate information (informed consent); accepting study participants' opinions and choices (autonomy), and protecting those who lack the capacity to function autonomously (diminished autonomy).

Justice. Fairness in the distribution of benefits and burdens.

Beneficence. Maximizing possible benefits and minimizing possible harm.[viii]

Outside of the professional and ethical responsibility to study participants, federal laws and regulations mandate two processes that specifically address the quality and safety of research processes, goals and objectives. More importantly, these two processes 1) Institutional Review Board Approval and Monitoring, and 2) Informed Consent play a key role in supporting study participants' safety.

An **Institutional Review Board** (IRB) is a committee formally designated by an institution to review, approve the initiation of and conduct a periodic review of biomedical research involving human subjects.[ix] The IRB is responsible to ensure the safety, privacy and well-being of all study participants throughout the research process and should be established, operated and function in conformance with *21 CFR 56*. IRB objectives include consideration of the following examples:

- Is the research consistent with the goals of the medical profession?
- Does the research focus on answering questions that will contribute meaningfully to medical knowledge and practice?
- Is the clinical trial well designed to yield valid data?
- Does the protocol include criteria for discontinuing the study?

- Are the risks appropriately minimized without compromising scientific integrity?

The **Informed Consent** process is used universally to inform patients of the risks, benefits and alternatives to a recommended treatment. With respect to research, informed consent is an essential safeguard that respects and supports study participants' autonomy, allowing the individual to decide whether to volunteer to participate in research.[x] A suitable consent process should identify the following:

- Any known risks or foreseeable hazards
- The likelihood of therapeutic or other direct benefits for the participant
- Alternative options open to study participants, including choosing standard or no treatment instead of participating in the study.[xi]

In addition, study participants should be provided an opportunity to ask questions and consider all options in an unbiased and supportive environment.

IRB oversight and the Informed Consent process, along with EVCR and EVSI oversight support study participants' safety, and the principal investigator's significant role and overall responsibility for the clinical trial.

CLINICAL RESEARCH

Envision Healthcare's Clinical Research Department (EVCR) provides support and guidance for Envision-affiliated physicians interested in participating in clinical research. EVCR engages in business development activities in partnership with industry sponsors, aligns with sponsors' research pipelines and uses many avenues and approaches to conduct business development. Business development efforts focus on "new leads" and physician-specific interests. For every active clinical trial managed by the department, EVCR team members participate in and support legal approval, budget and contract negotiations and protocol feasibility. The principal investigator (PI), in tandem with EVCR, is highly involved and serves as the initial decision-maker in the assessment of new leads and determining whether a trial is accepted or denied. The EVCR team stays highly engaged with the PI from start-up, through Institutional Review Board (IRB) submission, facility logistics planning, on-site operations and the duration of the trial. Research is a complex process with significant regulatory, financial and ethical implications. The scope of a clinical trial is substantial and includes EVHC, facility and sponsor processes;

staff from the involved organizations; financial planning and management; and patient education, monitoring and support.

Communication between the research team, PI and facility are primordial to the quality of every clinical trial and necessary in our research model of conducting research as contractors and as a value-added activity with our partnering facilities. Figure 1 (page 12) provides high-level insight into the complexity of clinical research.

10/17/18
Claudia Gomes, Director EVCR and EVSI accepts the Site Tank Award on behalf of Envision Healthcare's Clinical Research Department.

EVCR has best practices for ensuring research integrity and the safety and well-being of study participants in Envision-approved internal and external research programs (Appendix C, page 19). The purpose of these best practices is to:

A. Provide guidance to clinicians for compliance with federal regulations for the protection of study participants participating in research that EVCR conducts or supports.
B. Allow EVCR to communicate our commitment to protect the rights of all study participants.
C. Explain appropriate procedures to support study participants involving interventions or interactions to ensure high quality and data integrity.
D. Define specific responsibility of the PI, sub-investigator, Envision physician providing a standard-of-care service to study participants, and all personnel participating in planning, reviewing, executing or administratively supporting research involving study participants.

EVCR personnel are responsible for supporting the PI, as well as the clinical and operational aspects of the trial. EVCR roles and responsibilities throughout the clinical trial are summarized to the right. Clinician participation in clinical trials is pivotal to the advancement of new and innovative treatments. EVCR is committed to providing ongoing opportunities and support to our clinicians in their pursuit to deliver high quality, effective and cutting-edge clinical care to patients and to actively engaging in efforts to improve the quality and safety of healthcare.

EVCR's Role and Responsibilities:

- Feasibility Protocol Completion
- Contract Negotiations
- Budget Development
- IRB Submission
- Education/Training
- Patient Visits
- Data Collection and Analysis
- Communication Support Between Stakeholders

SCIENTIFIC INTELLIGENCE

Envision Healthcare's Scientific Intelligence Department (EVSI) supports clinicians interested in studying novel research ideas, including unique research studies with scientific and business merit. EVSI support includes assisting investigators with study design, performing statistical analysis, completing IRB approval and project execution through professional publication. In contrast to EVCR, most investigator-initiated trials (IITs) originate from, and are funded and fully managed by, a non-pharmaceutical researcher — the sponsor investigator (SI) — with EVSI as the sponsor. Following FDA regulations, the investigator assumes the responsibility of both a sponsor and an investigator for all IITs. The expectation is that all studies will be conducted following GCP and ethical principles with oversight by EVSI.

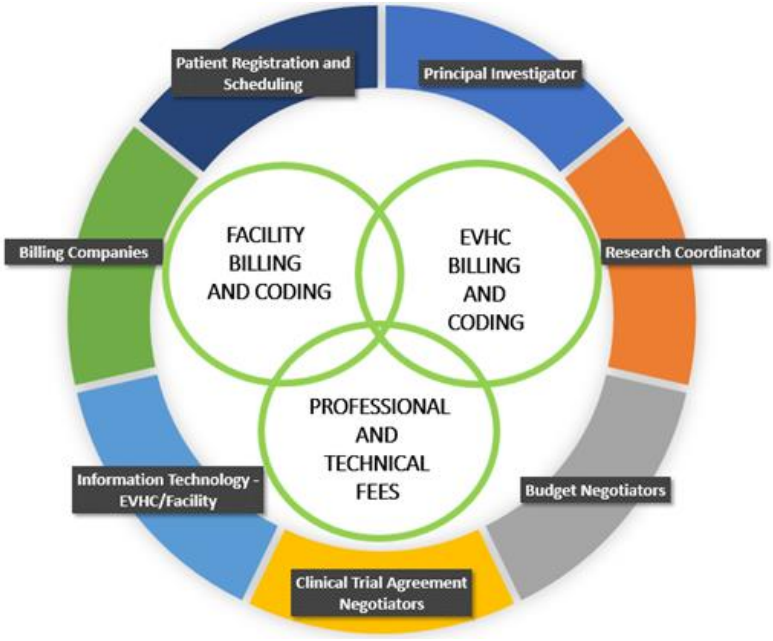
The purpose of EVSI can be viewed as two-fold. The investigator may partner with a pharmaceutical company without the company taking the role of sponsor as defined by the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH-GCP), or the investigator may conduct their own IITs without company involvement. What drives the need for EVSI to conduct IITs? The improvement of general population health, large patient data sets and the opportunity to be a part of cutting-edge research. Improved patient health and access to new treatments are a direct result of IITs that lead to the expansion of product knowledge, both clinical and observational (data only studies). Furthermore, IITs provide the investigator the opportunity to study existing treatments in new indications, to further understand product safety and to initiate their own post-market research.

EVSI support and expertise includes:

- Ensuring objective, ethical and responsible conduct of research
- Providing support and guidance with the investigator-initiated study design, formulation and execution
- Assisting with preparation of study protocols and submission to regulatory entities securing protocol approval prior to initiation of the study
- Helping prepare investigator abstracts, white papers, manuscripts, meeting presentations, industry-sponsored grants and statistical analysis of study results
- Providing financial support for the most meritorious studies pursued by our investigators

BILLING COMPLIANCE

FIGURE 1: BILLING *TAKES A VILLAGE*



Billing healthcare claims is extremely complex and involves numerous members of the healthcare team and departments. See Appendix H (page 25) for a detailed analysis of the billing process. As explained below, billing for routine clinical services as opposed to billing for the same services under the umbrella of research requires a different process.

Billing compliance becomes increasingly challenging when facilities engage Envision-affiliated clinicians in research without going through EVCR's approval process. In these instances, critical knowledge surrounding the clinical trial's budget and the principle investigator's role is unknown to EVCR. This may result in the inadvertent categorization of professional fees tied to clinical research, which the EVCR will need to correct. Billing that requires correction can also affect the patient, creating inappropriate bills and distrust and negatively affecting the patient experience. For these and many other reasons, it is imperative that EVCR be aware of and provide oversight for all clinical research activities involving affiliated clinicians.

BEST PRACTICE RECOMMENDATION: Clinician or facility engages EVCR once the clinical trial is awarded by the pharmaceutical company.

SECONDARY PRACTICE RECOMMENDATION: Clinician or facility notifies EVCR at the time of *budget and contract* negotiation.

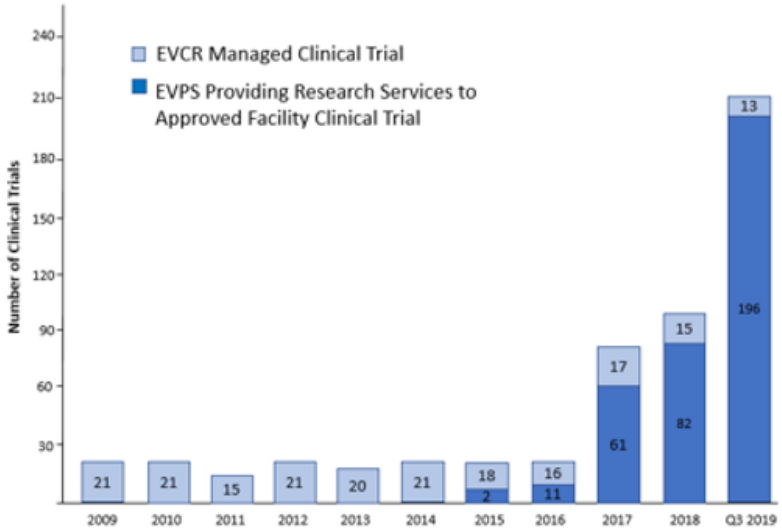
Envision Healthcare is committed to complying with all applicable federal rules, regulations and laws and to applying best practices in coding and billing. EVCR complies with the Centers for Medicare & Medicaid Services Clinical Trial Policy (CMS-CTP) across all activities including all approved clinical trials conducted by EVCR, partner facilities and community physicians. Compliance with regulatory guidelines remains a critical component of EVCR's program.

EVCR and EVSI have appreciated significant growth over the past two years. Appendix G (page 23) provides a timeline of program development and growth. As EVPS continues to grow and the number of clinical trials — the majority of which are managed by our partnering facilities — continues to expand, it is of utmost importance that we work together to correct deficiencies, eliminate communication silos and mitigate risk.

RESEARCH ETHICS AND COMPLIANCE TRAINING

Good Clinical Practice (GCP) refers to compliance with regulatory guidelines while conducting a clinical study. The regulations apply to manufacturers, sponsors, clinical investigators, key study personnel and IRBs. The conduct of clinical trials is governed by *Title 21, Code of Federal Regulations (21 CFR*).

FIGURE 2: RESEARCH GROWTH BY YEAR



Prior to conducting research, EVCR requires all clinical investigators to complete training on *Good Clinical Practice (GCP) – GCP for Clinical Trials with Investigational Drugs and Medical Devices (FDA Focus).* Every two years EVCR requires a GCP refresher course for training maintenance. Facility-based requirements that align with or supersede EVCR's requirements may be completed in lieu of EVCR training. The Collaborative Institutional Training Initiative Program (CITI Program) offers the initial and GCP refresher courses, as well as other valuable courses related to clinical research including *Human Subject Protection, Biomedical Basic* and *Conflicts of Interest*. Additional information is available at CITI Program.

LEGAL CONSIDERATIONS

Clinical research is highly regulated by the U.S. Food and Drug Administration (FDA). For every clinical trial conducted by EVCR under these regulations, there is a clinical trial agreement (CTA) between the study site and the study sponsor or clinical research organization (CRO). The CTA is provided to our central research office by industry sponsors. At EVCR, there is a well-established process for CTA review to ensure legal protection. The legal team that reviews all EVCR studies clearly understands what they are agreeing to before approving the CTA.

In 2018, Envision's legal department finalized research legal language to cover our physicians' involvement in facility-run clinical trials, where the facility holds the CTA, not EVCR, to be included in services agreements. The legal department is working to include this language in services agreements where appropriate. The purpose is to raise awareness of the risks involved in clinical research and the fact that research risks are not covered by our general facility agreements. There are many other reasons EVPS and our facilities involved in research need to build a stronger research communication pathway:

- **Facility may be paid by the clinical trial directly for EVPS services while EVPS is unaware and billing for clinical care.**
- **EVHC is not indemnified if not notified.**
- **Fair Market Value (FMV) determinations when sponsor is paying for a service, and EVHC has to invoice facility instead of Medicare/third party for clinical care.**

Legal considerations include consideration with respect to our patients, the research volunteers. The basic ethical principle of research is minimizing the risk of harm, and this occurs upstream at study design. The major ethical principles during the conduct of research are informed consent, beneficence, respect for confidentiality and respect for privacy.

Informed consent for a clinical trial typically includes more information than the consent for standard treatment. According to U.S. regulations and *21 CFR 50 Subpart B* - Informed Consent of Human Subjects, no informed consent releases the investigator, sponsor or facility from liability for negligence and carelessness. Note that the informed consent for clinical trials continues for as long as completion of all protocol-required safety data is collected, which can be years. Proper legal oversight of all research

activities involving Envision Physician Services is key. Legal review, approval and execution of all legal documents is a requirement. The major points reviewed by Legal for your protection and the protection of the organization are indemnification, confidentiality, subject injury, intellectual property and publication rights.

It is important to note that EVCR has been a member of the Society for Clinical Research Sites (SCRS) since it was established in 2012. With SCRS and TransCelerate, a non-profit organization also launched in 2012 to improve the health of people by simplifying and accelerating research and development, EVCR (formerly Sheridan Clinical Research) participated in the Common Language Evaluation and Reconciliation (CLEAR) initiative from 2014-2016. The CLEAR initiative is a national initiative to speed up legal contract review so research sites can begin enrolling patients in need of that clinical trial in a more streamlined manner and with less wait time for treatment. For sponsors that have also adapted this initiative, CLEAR language generally resonates in many EVCR CTAs as it was also adopted by our organization for CTA negotiations.

APPENDIX A: RESEARCH TESTIMONIALS

"… we recognize that without patients who are willing to participate in clinical trials, there would be no trials or treatments. Envision Healthcare recognizes the courage of these individuals and is grateful to them for their engagement with us, for their trust in us, and for their support of our mission to enhance the care of our patients, their families and communities nationwide."

"The trial study experience was very good. It was very informative and helpful; everyone was so nice. I'm glad to have been a part of something so important to women's health." — V.C.

"My experience with the team and the product was great! Something so private and intimate that I normally would not want to discuss was taken seriously and professionally. I was not only provided with treatment to help physically and sexually but also emotionally and mentally. Thanks so much for all the support and service." — S.W.

"…the wonders of modern medicine are a direct result of medical research. Being involved in research offers the clinician the satisfaction of discovery and the honor of contributing to the care of those whom they will never know."

"I have been involved in clinical research for the past 40 years. I was introduced to clinical trials by my greatest mentor, my father, who was involved in clinical phase 1-4 trials. I witnessed firsthand the excitement of reviewing protocols; participating in the trials and seeing a drug approved and brought to market. I can honestly say I love making a difference in this world and working with a wonderful team of dedicated people that share my same passion." — Jay S. Cohen, M.D., FACOG

"My interest in research started when I was in medical school. I was impressed by the opportunities in the medical field to be on the cutting edge of new treatments and technologies. As part of my ongoing commitment to improving patient care through evidence-based medicine, I have been involved in clinical research studies for the past 10 years in the Department of Pediatrics and Neonatology. As a PI for clinical trials, I am excited to be involved in reviewing study protocols; assuring that patients receive appropriate study-related medical care; ensuring compliance with GCP principles; working with an exemplary research team; playing a crucial role in the development and advancement of drugs, therapies, medical devices for the betterment of patient outcomes; and reducing long term health system costs." — Jenitha Jeyaraj, M.D., FAAP

APPENDIX B: DEFINITIONS

Code of Federal Regulation (CFR): The codification of the general and permanent rules and regulations published in the Federal Register by the executive departments and agencies of the federal government of the United States. The CFR is divided into 50 titles that represent different areas, such as research, subject to federal regulation.

Collaborative Institutional Training Initiative (CITI): The CITI Program is a training program that satisfies Good Clinical Practice (GCP). GCP training is required for all individuals involved in the conduct of clinical trials in any of these categories: biomedical research, social-behavioral research and all research supported by the National Institutes of Health (NIH). CITI Program

Common Rule: The Common Rule is the federal policy for the protection of human subjects. The Common Rule was published in 1991 and codified in separate regulations by 15 federal departments and agencies. U.S. Department of Health & Human Services (HHS) regulations, 45 CFR part 46, includes four subparts — subpart A, also known as the Common Rule, outlines the basic provisions for IRBs, informed consent and assurances of compliance.

Food and Drug Administration (FDA): An HHS Agency that regulates clinical investigations of products under its jurisdiction, such as drugs, biological products and medical devices. FDA is not considered a Common Rule agency because its regulations differ from the Common Rule; however, FDA is required to harmonize with the Common Rule as permitted by law.

Good Clinical Practice: An international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve human subjects. This international quality standard is defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which governs clinical research and protects the rights and well-being of trial participants.

Grant: Financial support from government, industry, community agency or other entity to cover costs of an Envision Physician Services investigator-initiated research study over a specific period. Grant applications are submitted in response to specific requests for applications, funding opportunity announcements, or other mechanisms.

Human Subject: A living individual about whom an investigator (professional or student) conducting research obtains data and/or personal health information (PHI) through intervention or interaction (i.e. surveys) with the individual.

Institutional Review Board (IRB): A board, committee or other group formally designated by an institution to review, approve the initiation of and to conduct a periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights, safety and welfare of human subjects. The IRB should be established, operated and function in conformance with 21 CFR 56.

Investigational New Drug (IND): FDA program by which a pharmaceutical company obtains permission to start human clinical trials and to ship an experimental drug across state lines before a marketing application for the drug has been approved. Regulations that apply to the IND application process are under 21 CFR Part 312 (Investigational New Drug Application) and all actions are documented for all drug sponsors as required under federal law.

APPENDIX B: DEFINITIONS (continued)

Investigational Device Exemption (IDE): Allows an investigational device (i.e. a device that is the subject of a clinical study) to be used in order to collect safety and effectiveness data required to support a premarket approval (PMA) application or a premarket notification (510k) submission to the FDA. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluation of investigational devices, unless exempt, must have an approved IDE before the study is initiated.

Investigator-Initiated Research/Study: Research, in which the investigator designs, implements, conducts and oversees all aspects of the research study.

Key Study Personnel: Individuals who contribute to the research study and team in a substantial way, such as the contribution of study data and participation in the conduct of a study.

Principal Investigator (PI): A PI is the primary individual responsible for the preparation, conduct and administration of a research grant, cooperative agreement, training or public service project, contract or other sponsored project in compliance with applicable laws and regulations and institutional policy governing the conduct of sponsored research. As a PI, this individual is ultimately responsible for all aspects of a clinical research trial.

Quality Improvement (QI): A project intended to facilitate immediate, continuous healthcare delivery, professional development, system performance and/or patient outcomes improvement in specific settings through methodical, efficient, data-driven activities.

Research Site: The research site is the physical location where the patients are seen for procedures that occur as part of the conduct of the research program investigation. The research site can be an office-based facility or hospital facility.

Research: A systematic investigation that entails the collection of data, documentation of critical information and analysis and interpretation of that data/information in accordance with methodologies set by specific professional fields and academic disciplines. Research methods can be one of two: qualitative or quantitative. Both methods are conducted in compliance with all applicable federal, state and local policies and regulations.

Statement of Investigator (Form FDA 1572): An agreement signed by the PI to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic. The PI should complete the form as accurately as possible and be aware that making a willfully false statement is a criminal offense under 18 U.S.C. 1001 and can lead to the disqualification of an investigator.

Sub-Investigator or Co-Investigator (Sub-I/Co-I): A Sub-I or Co-I can be one or more key study personnel who have responsibilities like that of a PI on a clinical research trial. While the PI has ultimate responsibility, the Sub-I/Co-I is also obligated to ensure project compliance with applicable laws, regulations and institutional policy governing the conduct of sponsored research.

APPENDIX C: EVCR VISUAL PROCESS STEPS

Opportunities and Industry Partnership	• BD • Research Conferences • Investigator Sign-ups
Industry-Sponsored Opportunity	• 1. CDA reviewed and executed • 2. Protocol shared for reviews by CR and physicians • 3. Sponsor feasibility questionnaire completed by CR and proposed PI (time-sensitive/competitive) • 4. Info on patient population and equipment reported • 5. Feasibility questionnaire is submitted to sponsor and tracked by CR
Sponsor Requests a Pre-Site Visit	• CR works with Sponsor, Proposed PR, and facility to schedule date • Sponsor conducts visit and within 2 weeks provides notification on site selection • Site Selection letter initiates next steps
Envision CR Unique Feasibility Tool	• Feasibility Tool is completed by Research Coordinator and PI (Full protocol required) • Protocol procedures are assessed by PI for feasibility and frequency for the purpose of budget negotiation • Coverage Analysis is completed by Clinical Research Manager and approved by Clinical Research Director • Billing guide and billing compliance plan to be carried out during the study is dictated by the Coverage Analysis
Contract Phase	• Site selected: Sponsor sends CR the Clinical Trial Agreement containing budget • Clinical Trial Agreement is sent to Legal for review, negotiation and execution • CR negotiates and finalizes budget
Institutional Review Board (IRB)	• Site selected: Sponsor sends CR the Regulatory packet (latest protocol, ICF, Regulatory documents) • Informed Consents is reviewed of EVCR specific changes • IRB submission form (Central or local) is completed and submitted for review along with ICF • IRB approval is received and filed in Regulatory Binder at the Site.
Training and Site Initiation	• EVCR required training through CITI Program and sponsor protocol-specific training is completed prior to any study procedure being conducted • EVCR team conducts "in-services" at the facility to train and document facility personnel involved in the study. • Sponsor conducts Site Initiation Visit (SIV) to ensure the two steps above and document their own training efforts • Site is ready to start enrollment and starts screening patients for inclusion
Study Accrual/ Enrollment	• Reearch Coordinator works closely with facility and/or office for identification of potential qualified subjects • PI or other delegated study personnel initiates informed consent proces: patients enoll or deny participation • Sponsor Rep. conducts interim monitoring visits to check quality and protocol compliance • Sponsor communicates status of enrollment phase in terms of volume of patients enrolled collectively at all sites • Sponsor communicates end of enrollment phase (Current patients stay to finish all study visits)
Study Closure	• All enrolled patietns have completed all study visits • Sponsor representative conducts Close-Out Visit (COV) and hard data lock. • EVCR submits study closure to the Institutional Review Board (IRB) • EVCR keeps all study documents for time period specified in Clinical Trial Agreement and as specified in EVCR Standard Operating Procedures (SOP) prior to sending to Iron Mountain for long-term storage
Protocol Proposal Review: Score 17 or Below	• EVSI sends written notification of disapproval (see Process for more details on EVSI role) • EVSI sends Protocol Rating Rubric with scores; highlight deficiencies • Ensure PI understands Protocol Proposal must be revised/resubmitted
Conflict of Interest Review	• EVSI reviews Investigator RCOI information; obtains missing information and clarifies conflicts • If Conflict of Interest identified, send Investigator RCOI Form • If needed, send Investigator RCOI Management Plan (see Process for more details on EVSI role)

APPENDIX D: EVSI VISUAL PROCESS STEPS

Clinician EVSI Contact	• Primary Investigator (PI) contacts EVSI with interest in research, or • EVSI contacts interested clinician
EVSI E-mails Documents to Primary Investigator	• Investigator-Initiated Research Study Proposal • Investigator-Initiated Research Protocol Proposal Rubric • Investigator Research Conflict of Interest Certification (RCOI) **BEST PRACTICES**
Document Notes: Protocol Proposal Form	• Form 1 for retrospective, observational, cross-sectional studies, etc. • Form 2 for clinical trials
Document Notes: QI vs. Research Checklist	• If purpose of project is unclear, send: • Quality Improvement (QI) vs. Research Study Information and Checklist
Document Notes: Study Timeline	• If timeline is needed, send: Principal Investigator-Initiated Research Study Timeline
EVSI Regulatory Analyst Emails CITI/CV Instructions to PI	• EVSI Regulatory Analyst alerted to new PI by EVSI • Sends PI CITI and CV information/requirements.
EVSI Reviews PI Documents	• PI completes all forms and returns to EVSI • EVSI reviews all forms
QI vs. Research Checklist Review	• If completed, EVSI reviews Research Checklist before proceeding • If Research, proceed with research document review • If QI, email PI with explanation of why project is QI (from QI vs Research Checklist). EVSI research support ends
Protocol Proposal Review: Score 18 or Above	• EVSI reviews Investigator-Initiated Research Study Proposal, rates Investigator-Initiated Research Protocol Proposal Rubric • EVSI sends written confirmation of approval (see Process for more details on EVSI role)
Protocol Proposal Review: Score 17 or Below	• EVSI sends written notification of disapproval (see Process for more details on EVSI role) • EVSI sends Protocol Rating Rubric with scores; highlight deficiencies • Ensure PI understands Protocol Proposal must be revised/resubmitted
Conflict of Interest Review	clarifies conflicts • If Conflict of Interest identified, send Investigator RCOI Form • If needed, send Investigator RCOI Management Plan (see Process for more details on EVSI role)
EVSI Prepares/Assists with IRB Submission	• EVSI emails PI-Initiated Research Study Checklist Note: experienced investigators will not require this form • PI returns form to EVSI for review prior to IRB submission
Publications/Presentations	• EVSI emails appropriate service line Conferences & Journals spreadsheet (see Process for note on spreadsheets) • EVSI reminds PI that all publications/presentations must be approved by EVSI prior to final submission

APPENDIX E: ENVISION CLINICAL RESEARCH RECEIVES NATIONAL RECOGNITION

The Society for Clinical Research Sites (SCRS) announced to nearly 1,000 attendees at their 2018 Global Site Solutions Summit that Envision Physician [Services] Clinical Research won the 2018 Global Site Tank Award.

The Site Tank Award recognizes a research site for creating innovative technology solutions for clinical research. Three finalists were chosen by an independent judging panel to present their innovation at the Global Site Solutions Summit held in Boca Raton, FL, from Oct. 11-14. Clinical Research and Scientific Intelligence Director Claudia Gomes, representing Envision Physician Clinical Research, received the award for the group's new innovative dashboard created to track clinical trial activity across our many facilities and ensure research-billing compliance. Gomes said the platform helps keep track of new research activity as Envision Physician Services participates in research with existing and newly acquired facilities.

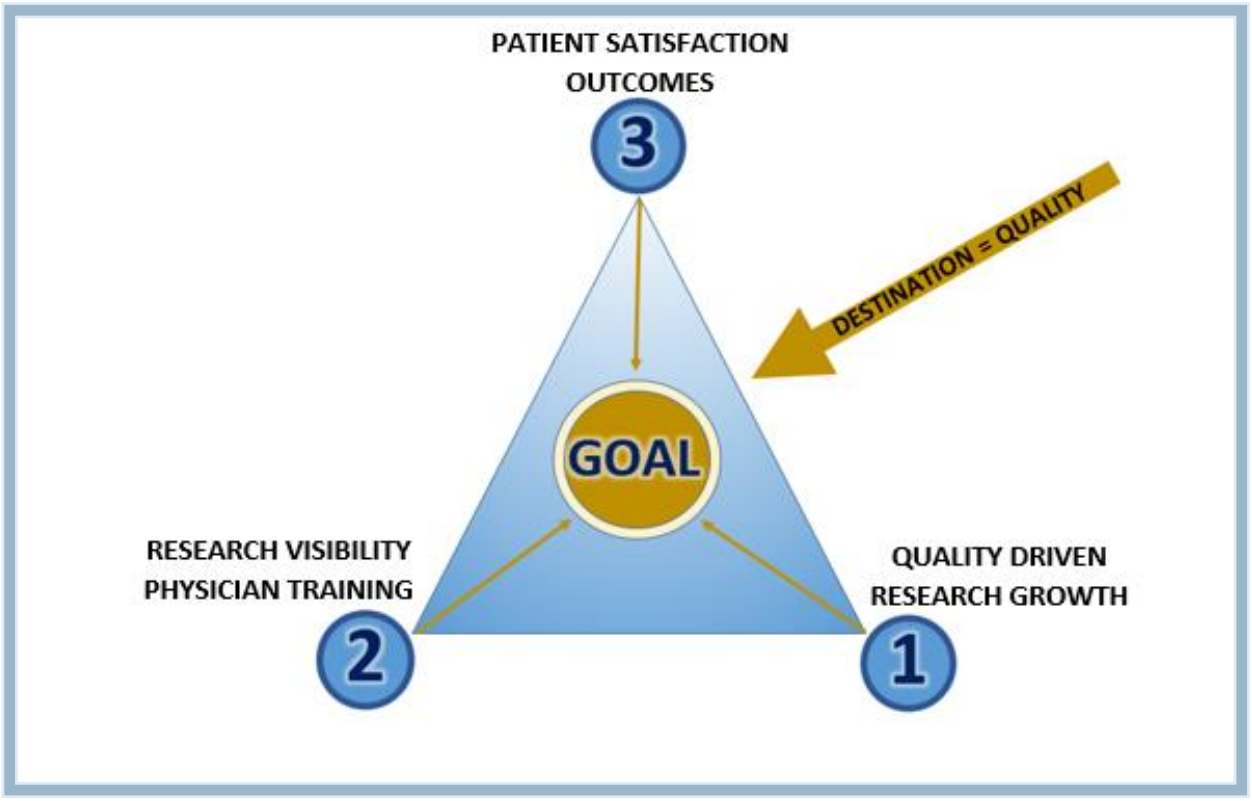
"The dashboard helps organize our clinicians and entities involved in different clinical studies. In the future, we want to have this interactive tool online on our research page where everyone can use the dashboard as a visual to see real-time metrics," Gomes said. "How many studies are we doing? Who are the clinicians involved, and at which facilities? This dashboard helps us keep track of this information."

The Site Tank Award relies upon judges' questions and the audience to select a winner with the most innovative and impactful technology solutions for clinical research. When assessing each presentation, judges looked for technology concepts designed to enhance, empower and improve the clinical research industry.

"Participation in … Site Tank is an opportunity for site excellence to be recognized by a large group of clinical research stakeholders who have come together to affect change," said SCRS late president Christine Pierre. "We are inspired by the innovation displayed by all who submitted recruitment and technology plans for … Site Tank consideration. Congratulations to … Envision Physician [Services] Clinical Research."

If you are interested in participating in clinical research, please contact Claudia Gomes at claudia.gomes@shcr.com or 954.939.7729 for further information.

APPENDIX F: EVCR TRIFECTA MODEL

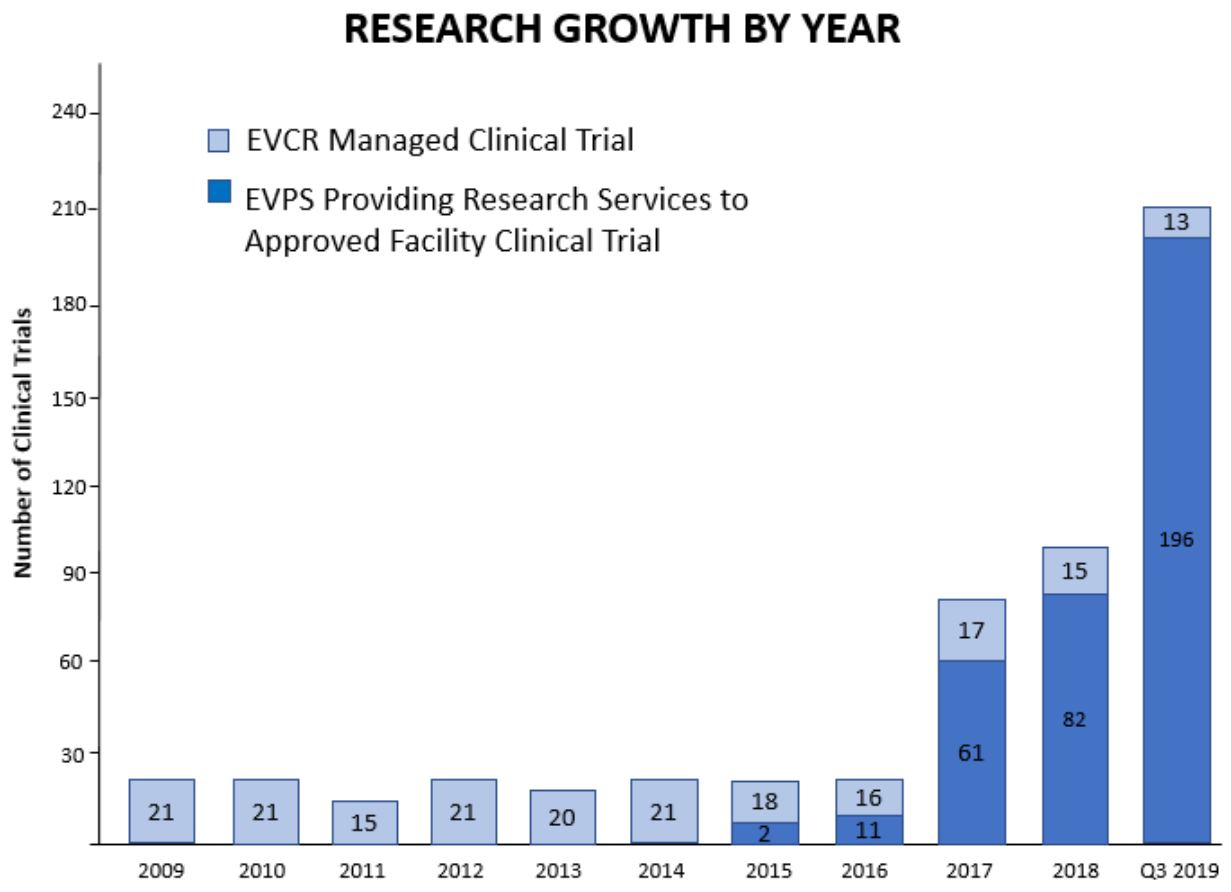


The Trifecta model demonstrates EVCR's primary goal of tying together quality-driven research growth, increased research visibility and patient satisfaction. The Trifecta is a balanced trio of activities that lead to success and results that have a positive impact on EVCR's social responsibility to deliver high-quality research to the community.

APPENDIX G: EVCR AND EVSI PROGRAM DEVELOPMENT AND GROWTH

ABOUT US

- Full-service department matches pharmaceutical-sponsored clinical trials to clinicians' areas of interest
- Physician leadership with greater than 25 years of investigator experience
- Supports the clinical trial and PI from inception through trial completion
- Facilitates regulatory submissions, contract and budget negotiations
- Provides on-site study coordinators according to need and management solutions
- Infrastructure to ease the burden of clinical trial paperwork, allowing physicians to spend more time with patients
- Robust billing compliance processes
- Promotes and assists with professional publication development and submission



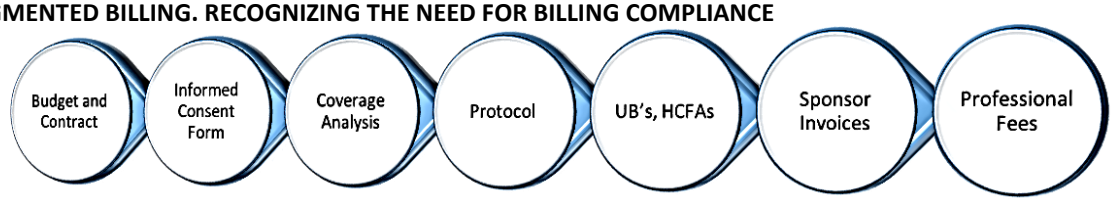
APPENDIX G: EVCR AND EVSI PROGRAM DEVELOPMENT AND GROWTH (continued)

Development Timeline

- 2000 – Envision Clinical Research Department (EVCR) is established
- 2000 – Deena Bernstein joins EVCR (formerly Sheridan Clinical Research) as clinical research director
- 2009 – Claudia Gomes joins EVCR (formerly Sheridan Clinical Research) as clinical research manager
- 2010 – EVCR becomes founding member of the Southeast Florida Chapter of the Association of Clinical Research Professionals
- 2012 – EVCR becomes member of The Society for Clinical Research Sites
- 2015 – Gerald Maccioli, M.D., joins EVPS as chief quality officer and medical director of program
- 2016 – Claudia Gomes is promoted to program director
- 2016 – Envision Scientific Intelligence Department (EVSI) is established
- 2016 – Jana Barlic-Dicen, Ph.D., joins EVSI as investigator-initiated research manager
- 2017 – Aubrey Florom-Smith, Ph.D., RN, joins EVSI as investigator-initiated research manager
- 2017 – Sloane Smith-Saunders joins EVCR as clinical research manager
- 2018 – The number of clinical research trials exceed 100
- 2018 – Lisa Ryan-Swartz joins program as clinical research manager (billing compliance)
- 2019 – Sara Sigler, Ph.D., joins EVSI as investigator-initiated research manager
- 2019 – The number of clinical research trials doubles compared to 2018

APPENDIX H: BILLING COMPLIANCE

FRAGMENTED BILLING. RECOGNIZING THE NEED FOR BILLING COMPLIANCE



Billing healthcare claims is extremely complex and involves numerous members of the healthcare team and various departments across the spectrum. The fragmented acquisition of information needed to complete compliant billing and the disparity between billing for routine clinical services as opposed to billing for the same services under the umbrella of research poses significant challenges.

To ensure compliance with billing rules and regulations, EVCR conducts a Medicare Coverage Analysis (MCA) for every clinical trial in which an EVPS-affiliated clinician is the principal investigator. The MCA is essential to determine who (i.e. sponsor, insurance, Medicare) is responsible for covering which costs. In addition, EVCR created a billing guide, which further delineates who is responsible for each clinical service. This guide should be shared with all members of the research and billing teams to support proper billing and ensure patients are only billed for services within their financial responsibility.

Research Versus Non-research Billing

Medical claims are starkly different between research and non-research patients. A physician may provide the same service to a research patient and a non-research patient, follow routine care and treat these two patients the same – the **common denominator**. The *differentiator* (in research claims) only surfaces at the time of billing – the **challenge**. The differentiator, required for research billing, has several elements including a National Clinical Trial (NCT) Identifier followed by an 8-digit number that needs to be included in the HCFA forms. Not only do these elements have to be present for timely filing, they also have to be in the proper locations. Otherwise, Medicare will not recognize the service provided as part of a clinical trial.

Medicare and other payers may reimburse for routine items and services provided in conjunction with a clinical trial. For example, Medicare pays for a hospital stay that they would normally pay for even if the patient was not in a clinical trial, but may not cover the cost of an operation to implant an investigational device or treatment for research-related complications. Insurance may not cover certain trial-related costs. For example, procedures done more frequently than required per routine care may not be covered by the insurer.

APPENDIX H: BILLING COMPLIANCE (continued)

GUIDELINES FOR COMPLIANT BILLING[xii]

- Perform a "Billing Coverage Analysis" **before** the study budget is developed; the Clinical Trial Agreement (CTA) is negotiated and signed and before any subject is registered in the trial.
- Determine payers for trial services.
- Create a billing grid and reconcile bills/invoices before submission to Medicare or Insurance Companies.
- Carefully follow policies/procedures for the registration and tracking of all research subjects.
- Notify all physician groups, hospitals, laboratories or other entities that may provide services to an enrolled research subject.
- Audit claims prior to submission to assure the technical and professional components (for the same service, same patient, same protocol) have mirror-billing elements.
    - Includes NCT#, IDE/G#, Q0 (investigational)/Q1 (routine care) and secondary diagnosis code Z00.6 for both technical and professional claims.
    - Excludes "condition codes" that are only seen on technical claims.

DOCUMENTS NEEDED FOR COMPLIANT BILLING

• Study Protocol
• Billing Coverage Analysis
• Contract Trial Agreement (CTA)
• Study Budget
• Informed Consent

REMEMBER

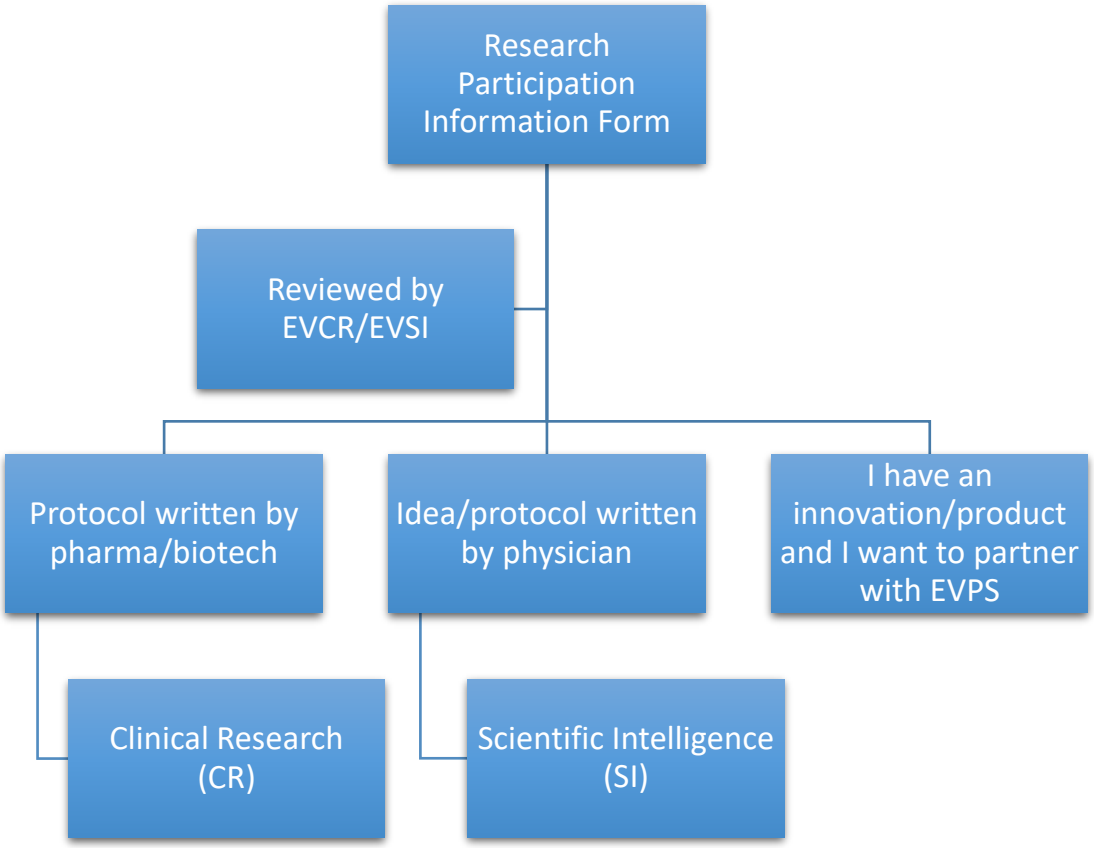
- Do not bill for services the sponsor is paying for
- Do not bill for services promised as free
- Do not bill for services that are for research purposes only
- Do not bill for services in a research study that is not designed to have therapeutic benefit
- Only bill for services that have no external funding source and are medically necessary

Figure 3 (following) provides process guidelines to follow regarding notification of and oversight by EVCR for Envision affiliated clinicians, facilities contracted with Envision Physician Services, community physician investigators and sponsors interested in participating in research or already conducting research, and require EVCR oversight to establish compliance.

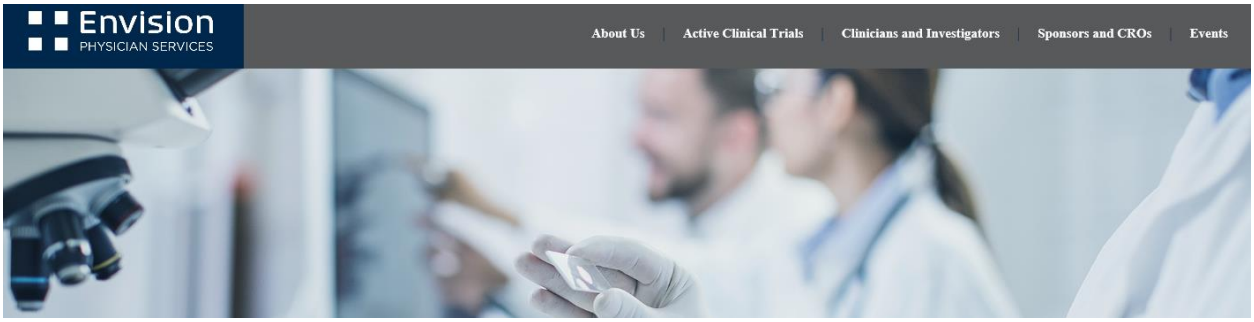
APPENDIX H: BILLING COMPLIANCE (continued)

For submitting interest or to report research activity, the Research Participation Form referenced below is available on the Clinical and Scientific Research website.

FIGURE 3: I am a Clinician/Facility and I Want to do Research



APPENDIX I: CLINICAL AND SCIENTIFIC RESEARCH



Website:
https://www.envisionphysicianservices.com/clinical-research

About Us:
Research Leadership

Contact Information:
E-mail: Claudia.Gomes@shcr.com
Phone: 954.939.7729
Contact Us

Resources Links:
Active Clinical Trials
Research Participation Information Form
Clinical Research - Envision Publications Form
CITI Program

APPENDIX J: REFERENCES

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[vii] *Id.*

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[x] American Medical Association – Code of Medical Ethics Opinion 7.1.2

[xi] *Id.*

[xii] Medical Billing for Research and Clinical Trials
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