Ethics/Regulatory Call with Dr. Jarvik's Demonstration Project - LIRE
Date: May 16, 2013
MINUTES

Participants:

☒	Jeremy Sugarman (Johns Hopkins)	☒	Barbara Young (Group Health)	☒	Julie Kaneshiro (OHRP)	☒	Cheri Janning (Coord Center)
☒	Rob Califf (Duke)	☒	Heidi Berthoud (Group Health)	☒	Catherine Meyers (NIH)	☐	
☒	Jerry Jarvik (Univ Wash)	☒	Jerry Menikoff (OHRP)	☒	Jim Panagis (NIH)	☐	
☒	Katie James (Univ Wash)	☒	Irene Stith-Coleman (OHRP)	☒	Amy Patterson (NIH)	☐	

These minutes were circulated to all participants on the call for two rounds of review and they reflect all corrections that were received.

AGENDA ITEMS	DISCUSSION	ACTION ITEM
Review of Demonstration Project	• Dr. Jarvik gave an overview of the LIRE project. The study's main hypothesis is that, for patients referred from primary care providers, inserting epidemiological evidence in lumbar spine imaging reports will reduce unnecessary subsequent diagnostic and therapeutic interventions, including cross-sectional imaging (MR/CT), opioid prescriptions, spinal injections, and surgery. • Sites: ▪ Group Health Cooperative (GHC) Site PI: Dan Cherkin, PhD ▪ Henry Ford Health System (HFHS) Site PI: Safwan Halabi, MD ▪ Kaiser Permanente of Northern California (KPNC) Site PI: Andy Avins, MD, MPH ▪ Mayo Clinic Health System (MCHS) Site PI: David Kallmes, MD	

Minimal risk	• The rationale for considering the project to be minimal risk was presented by the study team. • The rationale as presented by the study team is included in the appended document. • No objections or concerns were raised by participants regarding a minimal risk determination.	• A case study will be drafted to provide guidance for others wishing to evaluate similar decision support that does not direct therapy.
Consent (patient and physician)	• Justification for a waiver of consent was reviewed and no objections or concerns were raised by the group regarding it. • The rationale as presented by the study team is included in the appended document.	• This will be added to the case study.
HIPAA	• Dr. Jarvik feels that criteria for HHS Regulation 45 CFR 164.512 were satisfied and a waiver of HIPAA is acceptable.	• This will be added to the case study.
Monitoring and oversight	• The designated Safety Officer, Steven Atlas, MD has agreed to review study data at regular intervals for any safety concerns • The data safety and monitoring plan is not yet finalized but this will be done prior to the beginning of the study • Dr. Jim Panagis indicated that this approach is in compliance with NIH/NIAMS data and safety monitoring policies.	• Finalize the data safety and monitoring plan. • This will be added to the case study when it is complete.
Issues beyond the LIRE trial	• There was a brief discussion regarding decision support tools that include therapeutic recommendations. Several opinions were expressed that if the recommendations were within the standard of care for the condition being studied, minimal risk might still pertain, but not when recommendations extended beyond the standard of care. • No definitive conclusion was reached.	• Further discussion needed.
Conclusion of meeting	• All meeting participants felt that it was reasonable for the LIRE project to continue its planning activities for implementation.	

SUPPLEMENTARY MATERIAL FOR LIRE TRIAL

Lumbar Imaging Reporting with Epidemiology (LIRE)

Project Summary

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Lumbar Imaging Reporting with Epidemiology (LIRE)

The overall goal of our Pragmatic Trial of Lumbar Image Reporting with Epidemiology (LIRE) is to perform a large, pragmatic, randomized controlled trial to determine the effectiveness of a simple, inexpensive and easy to deploy intervention – of inserting epidemiological benchmarks into lumbar spine imaging reports – at reducing subsequent tests and treatments. The long-term public health significance is that our simple, inexpensive intervention has the potential to substantially reduce unnecessary and expensive care for back pain patients. Importantly, our approach could be applied to a wide range of other conditions and other diagnostic tests (e.g. other imaging tests, laboratory tests, genetic testing). If our study is positive, adding epidemiologic benchmarks to diagnostic test reporting could become the dominant paradigm for communicating all diagnostic information.

1. Participating Institutions:

1.1 Data Coordinating Center (DCC) and Prime Awardee:
University of Washington- Seattle, WA
Principal Investigator: Dr. Jeffrey G. Jarvik, MD, MPH

1.1 Performance Sites

1.1.1 Group Health Cooperative (GHC)- Site PI: Dan Cherkin, PhD
1.1.2 Henry Ford Health System (HFHS)- Site PI: Safwan Halabi, MD
1.1.3 Kaiser Permanente of Northern California (KPNC)- Site PI: Andy Avins, MD, MPH
1.1.4 Mayo Clinic Health System (MCHS)- Site PI: David Kallmes, MD

2. Project Overview

Our main hypothesis is that for patients referred from primary care providers, inserting epidemiological evidence in lumbar spine imaging reports will reduce subsequent diagnostic and therapeutic interventions, including cross-sectional imaging (MR/CT), opioid prescriptions, spinal injections and surgery.
To test our hypothesis, we propose to conduct a pragmatic cluster, randomized controlled trial, randomly assigning primary care clinics at four large health systems to receive either standard lumbar spine imaging reports or reports containing epidemiological benchmarks for common imaging findings. We will use a novel stepped wedge randomization scheme that temporally randomizes sites, allowing within-site before/after comparisons in addition to between-site comparisons, while assuring that all sites will eventually receive the intervention. Our primary outcome will be a metric of back-related intervention intensity. The

primary analysis will occur at the clinic level and not the patient level.
Our pragmatic trial will demonstrate both the feasibility of randomly assigning clinics within large health systems as well as the feasibility of passively collecting outcomes data up to two years after enrollment using the robust electronic medical records systems available at each health system.

2.1 Study Procedures

Using the site administrative data systems, we will identify all primary care providers (PCP) at a given clinic. When an identified PCP from a randomized clinic submits a request for a lumbar spine imaging study, the report will automatically be flagged. The PCP's name will be cross-referenced with the randomization assignment and those PCPs who work in clinics assigned to receive the intervention will have the epidemiological benchmark information automatically inserted into their imaging reports. Those PCPs who work in clinics not yet scheduled to receive the benchmark information will get the usual imaging report issued by their radiologists.
Since the intervention will be applied at the PCP and clinic level, all patients receiving lumbar spine imaging studies at those clinics will be part of the trial. The lumbar spine imaging studies that we plan to include in the trial are plain films, magnetic resonance (MR) imaging examinations and computerized tomography (CT).

2.2 Study Intervention

The intervention itself is a macro containing epidemiologic benchmark data to be inserted into the radiology report in a randomized fashion. Primary care physicians and patients (who access their medical records) will see the modified radiology report, thereby being exposed to the intervention. Individual patients and physicians will not be randomized in this study design. Rather, all lumbar imaging reports generated from orders placed by physicians at a given clinic will be randomized to receive the modified radiology report versus receiving an unchanged (usual care) report. By the end of the study timeframe, all radiology reports will contain the intervention macro and thus include epidemiologic benchmarks.
Below, is an example of language from a 2012 article published in the journal *Radiology* that is serving as pilot work for this project (full article can be found in Appendix I).

Comment: The following findings are so common in people without low back pain that while we report their presence, they must be interpreted with caution and in the context of the clinical situation. (Reference –Jarvik et al, Spine 2001)

Findings: (prevalence in patients without low back pain), Disk degeneration (decreased T2 signal, height loss, bulge) (91%), Disk T2—signal loss (83%), Disk height loss (56%), Disk bulge (64%), Disk protrusion (32%), Annular tear (38%)

3. Human Subjects

Because the intervention will be administered at the clinic level, consent of either individual patients or primary caregivers is neither feasible nor warranted. Moreover, the intervention is relatively benign (the insertion of additional epidemiological information into the radiology report) and poses minimal risk to caregivers and patients. Because leadership at the Healthcare Systems making up the performance sites are enthusiastic about incorporating the epidemiological benchmarks into their reports and may well eventually adopt them regardless of the project, our study simply allows us to systematically study the effects of a well-controlled implementation of the insertion of the benchmark information. The randomization scheme defines when each clinic begins including the epidemiological information into the reports, with all sites eventually receiving the intervention of interest.

3.1 Risks to Subjects

3.1.1 Human Subjects Involvement and Characteristics:
Eligibility criteria: A patient will be eligible for inclusion in the study if they are at least 18 years old and referred by their primary care provider for plain films, CT or MR of the lumbar spine to evaluate low back or leg pain. We will access patient medical records 6 months prior to the index image and for two years after the index image in order to track key variables before and after the intervention. Subjects will receive usual care, and neither their diagnostic evaluation nor their therapy will be constrained by study considerations. We anticipate enrolling ~100,000, patients who undergo lumbar spine imaging examinations across four different health systems.

3.1.2 ResearchData
Research data will consist of individual subjects' medical record data and information on clinics and providers. We will collect all data passively with automated data extractions. Data extracted from the medical record will include demographic data, variables related to imaging, pharmacy, procedures, hospitalizations, and other factors related to healthcare

utilization. We will not collect patient reported outcomes unless they are part of the medical record.

We will collect demographic data on primary care providers and will code the data in such a way that an individual practitioner is not identifiable. We will use patient data to derive pre- and post-randomization rates of spine related interventions (diagnostic imaging, opioid prescriptions, spine related procedures, physical therapy etc.) among a provider's patient panel.
We will code with a unique study identification number, without reference to patient or provider identity. The code key will be kept secured at the recruitment site, separate from the data. Only the site researchers will have access to the code key (not the researchers at the DCC).

3.1.3 Potential risks

The research activities in this trial are very low risk. Perhaps the most important risk is a breach of confidentiality of clinical information.

Individual subjects will not be contacted or consented for this project. No patient reported outcomes are being collected and so no patient interviews will be performed. The intervention is being administered at the clinic level; therefore, consent of either individual patients or providers is neither feasible nor warranted. Moreover, the intervention is relatively benign (the insertion of epidemiological benchmark data into the radiology report) and poses virtually no risk to either providers or patients. We will not constrain the choice of tests or treatments offered to subjects.

The main risk associated with this project will be loss of confidentiality as medical record access will be necessary in order to assess the impact of the intervention. We will make extensive efforts to assure that records are kept in locked files and are not identifiable to anyone but the investigators. All PHI will be stored securely locally. Non-PHI data will be uploaded via a web-based system to the Data Coordinating Center at the Center for Biomedical Informatics and Biomedical Statistics at the University of Washington. Anonymized data will be stored on a server located at Biomedical Informatics, where no names or hospital numbers are included and only study numbers will be attached to the data files. Data will be kept on a server that requires a password for entry and in a locked office.

As the identities and clinical information gathered on patients will be guarded, so too, will the identities and data collected on clinic providers. All identifying information will be stored securely at the local recruitment sites. Only coded, limited data set will be transferred to the DCC such that an individual provider from a given clinic within a health system; cannot be identified.

3.2 Adequacy of Protection Against risks

We anticipate that each site will work within their own health system to identify primary care clinics, primary care providers, and operationalize the technical aspects regarding the intervention. The intervention itself is the addition of epidemiologic data relevant to the imaging modality and age range of a given patient for whom a radiologic image was ordered. This data will be automatically added to existing radiology reports in the intervention group. The randomization schedule will be allocated at the clinic site rather than at the individual patient or provider level. Only group results will be reported.

Per Health and Human Services Policy for Protection of Human Research Subjects , Section 46.102.i: "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests". We believe our proposed intervention meets this definition.

The risk of inserting the epidemiological benchmark data is minimal. It is analogous to having normal ranges available when interpreting laboratory tests. There is a small risk that the primary care providers who see the intervention will downplay the importance of all imaging findings and be more likely to pursue a more conservative course of care, thus possibly steering patients away from care that might improve outcomes. Given the general over-diagnosis and over-treatment of back pain in the U.S., the risk of under-treatment is probably negligible.

The potential benefits are quite large. At a minimum, primary care providers and patients will likely become better informed about back pain. If the results of the pilot study are borne out, prescriptions for opioids could be significantly reduced. This is a class of drugs that is undergoing an epidemic of complications. There is also the potential of avoiding other unnecessary treatments. Finally, if patients who receive the information get more efficient care, the health care system could see a financial benefit.

We will seek a waiver of consent from the IRB's at each of the participating health care systems since the risk to individuals is minimal, the intervention is relatively benign and consent of patients and providers is not practical.

3.3 Potential Benefits of the Proposed Research to the Subjects

We believe that the risks to subjects are minimal and that the relevant knowledge gains may be great. Individual subjects in this study are not likely to benefit immediately from this new knowledge, although it could influence their subsequent treatment, and may influence the treatment of others with a similar condition. Knowledge of benefit (or lack thereof) will inform providers and patients in the future about the usefulness providing

epidemiologic context to radiologic results in the management of low back pain.

3.4 Importance of the Knowledge to be Gained

This study will assess the impact epidemiologic data (tailored to radiologic modality and age range of a given patient) has on treatment outcomes among those with low back pain in the primary care setting. Low back pain is prevalent, imaging is routinely used in its assessment and evaluation, and radiologic results can heavily inform providers' clinical decision making. Since the risks to research subjects are minor and there is the potential for improved patient management, this research should be pursued.

3.5 Data and Safety Monitoring

We will draft a data safety monitoring plan (DSMP) in the planning year and have already designated a Safety Officer, Steven Atlas, MD who has agreed to review study data at regular intervals for safety concerns.

4. Justification for Waivers of Consent and Waiver of HIPAA

Per the U.S. Health and Human Services Regulation 45 CFR 46.116(d), an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that 1) the research involves no more than minimal risk to the subjects, 2) the waiver will not adversely affect the rights and welfare of the subjects, 3) the research could not practicable be carried out without the waiver, and 4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

4.1 Justification for Waiver of Patient Consent

4.1.1 *The research involves no more than minimal risk to the subjects*

The intervention is relatively benign (the insertion of additional epidemiological information into the radiology report) and poses minimal risk to caregivers and patients. That is the probability and magnitude of harm and discomfort introduced by the intervention are less than that experienced during daily life for an average person (per the Office for Human Research Protections). There is minimal risk associated with a breach in patient confidentiality, as is the case in any research study. To further minimize this possibility, we will maintain strict confidentiality of data through multiple processes, including

stripping identifiers from data sources (and linking them to codes not associated with MRN, name, or other personal identifiers), maintaining the link only at performance sites, transferring no identifiers to the DCC, secure storage of written and electronic data, limited access to all data, and reporting of only aggregate results.

4.1.2 The waiver will not adversely affect the rights and welfare of the subjects

Neither the health, financial, or legal interests of patients (as research subjects) are adversely affected by wavier of consent as study participation poses only minimal risk.

4.1.3 The research could not practicably be carried out without the waiver

4.1.3a The pragmatic design of this study does not allow a practical and easily implementable means of obtaining consent from individual patients or providers. The intervention is to be deployed at the clinic level.

4.1.3b Given the large potential study population, it would not be feasible to obtain consent. The study sites are all large with a combined 128 clinics and close to 1,900 primary care providers who would participate in the project. Based on data from 2011, we are likely to have over 300,000 back pain visits during each 12-month study enrollment period. We estimate that 20%-30% of these visits will result in a lumbar spine imaging study, equating to 190,000-285,000 imaging studies during the project accrual period.

4.1.3c By informing primary care providers and patients of the study, we risk invalidating the results. If providers and patients are aware of the intervention but are allocated to the control group, they may nevertheless change their behavior.

4.1.3d The risk of contacting subjects is greater than the risk of the study procedures. The risk for breach of patient confidentiality increases when subject contact information is maintained for the purposes of contacting patients for their consent. It is our opinion that this increased risk far exceeds the risk to subjects associated with the insertion of epidemiologic data into the radiology report interpreted by their provider.

4.1.3e Alternative methods for obtaining consent are not feasible without increasing risk to subjects beyond the minimal risk introduced by deploying the intervention.

4.1.4 *Whenever appropriate, the subjects will be provided with additional pertinent information after participation*

It would not be appropriate to provide individual subjects with information about the study after their participation because there is no feasible mechanism by which to notify subjects (no contact information retained) and it would not be practical to do so given the large population.

4.2 Justification for waiver of Physician Consent

4.2.1 *The research involves no more than minimal risk to the subjects*

The intervention simply compiles information readily available in peer-reviewed literature to which all health care providers have access and reference to inform their clinical care.

4.2.2 *The waiver will not adversely affect the rights and welfare of the subjects*

Neither the health, financial, or legal interests of providers are adversely affected by waiving consent as study participation poses only minimal risk.

4.2.3 *The research could not practicably be carried out without the waiver*

4.2.3a The design of the study does not allow the possibility of obtaining consent. The pragmatic nature of this design relies on the ability to deploy the intervention according to a predetermined randomization schema and have its insertion automated such that it can be consistently inserted without interfering with clinical care.

4.2.3b The potential study population is so large that it would no be feasible to obtain consent. The study are composed of close to 1,900 primary care providers who would participate in the project

4.2.3c By informing primary care providers and patients of the study, we risk invalidating the results. If providers and patients are aware of the intervention but are allocated to the control group, they may nevertheless change their behavior.

4.2.3d Requiring informed consent may introduce systematic bias if the patients of self-selected providers are not enrolled, given that this is a health care system-wide intervention.

4.2.4 *Whenever appropriate, the subjects will be provided with additional pertinent information after participation*

While we will not maintain individual physician identifiers in any

recognizable way, it is our goal to have these results published in peer-reviewed journals easily accessible to practicing providers.

4.3 Justification for waiver of HIPAA

Per the U.S. Health and Human Services Regulation 45 CFR 164.512, the following three criteria must be satisfied for an IRB to approve a waiver of authorization under the Privacy Rule: 1) The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements: a) an adequate plan to protect the identifiers from improper use and disclosure b) an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and c) adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart. 2) The research could not practicably be conducted without the waiver; and 3) The research could not practicably be conducted without access to and use of the protected health information.

4.3.1 The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
4.3.1a An adequate plan to protect the identifiers from improper use and disclosure

The risk to subjects is minimal and limited to breach of patient confidentiality. To minimize this possibility, confidentiality of data will be strictly maintained through multiple processes, including:

- Limiting <u>who</u> has medical record access to research study staff who have signed a confidentiality agreement, been thoroughly trained, and have adequate knowledge regarding patient confidentiality.
- Limiting <u>what</u> is being accessed by ensuring that the information being extracted from the medical record is well-defined and limited in scope (See attached list of variables, Appendix III)
- Limiting <u>when</u> records are being accessed to the timeframe six months before and two years after the index image.

- Limiting <u>where</u> records are being accessed by confining access to the performance site, stripping identifiers from data sources, maintaining links only at performance sites and providing only limited data to the DCC (including dates of service).

Secure storage of written and electronic data will be ensured. Only aggregated, group results will be reported in any presentation, publication, or report generated from this research.

4.3.1b An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers

Link to identifiers will be maintained only at the performance sites and will be destroyed after data analysis and manuscript writing is complete (unless a date is otherwise specified by a performance site's IRB requirements). No identifiers or links will be transferred to the DCC other than limited data set elements including dates of service.

4.3.1c Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart.

Only study personnel who have signed a confidentiality agreement will have access to medical record data. Links to identifiers will not be transferred or stored at the DCC but will be retained at the performance sites.

4.3.2 The research could not practicably be conducted without the waiver

The potential study population is so large that it would no be feasible to obtain HIPAA authorization on each and every patient seen at a given Health Care System during the study period.
In order to obtain authorization from patients, each patient would have to be contacted. Gathering and retaining contact information poses greater risk to the subject than access to medical records given the precautions in place. The pragmatic nature of this trial is such that patient outcomes that are part

of the medical record, will be collected passively via large-scale data extractions.

4.3.3 The research could not practicably be conducted without access to and use of the protected health information

Patient data is needed to derive pre- and post-randomization rates of spine related interventions (diagnostic imaging, opioid prescriptions, spine related procedures, physical therapy etc.) among a provider's patient panel to determine what (if any) effect the intervention had on spine related care.