Fall 2017

Research News

Regulatory Changes Impact Research in 2018

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On January 19, 2017, the U.S. Department of Health and Human Services (OHRP) issued final changes to update current regulations for the Federal Policy for the Protection of Human Subjects (the Common Rule). This is the first significant update since the regulations were issued in 1991. Most of the new regulations go into effect January 19, 2018.

The intent of the "Final Rule," as these regulations are known, is to modernize the federal policy on human subject research and align the regulations with the changes that have taken place in research since the Common Rule was first implemented. Large databases, biospecimen repositories, electronic health records, and clinical research networks have spurred new kinds of research. In addition, the internet, mobile technologies and the growth in computing power have changed the scale and nature of information collected. The revisions are intended to better protect human subjects, facilitate research (particularly minimal risk research), remove ambiguity, and reduce regulatory burden.

What are some Major Changes?

- The requirement for clearer, more focused consent forms to provide potential research subjects with a better understanding of the project's scope, including its risks and benefits, so they can make a more fully informed decision about whether to participate. The revised regulations require a concise explanation of the important aspects of the research at the beginning of the consent document, and include requirements for several additional pieces of information to be shared if applicable, i.e. whether biospecimens will be used for commercial profit, whether research may include whole genome sequencing, whether clinically relevant results will be disclosed.
- Requirements, in many cases, to use a single institutional review board (IRB) for multi-site research studies (effective January 20, 2020). However, institutions may still review for their own purposes.
- Elimination of the requirement to conduct continuing review of ongoing research where such review does little to protect subjects, i.e. expedited research and studies that have completed study interventions and are merely analyzing study data or involve only observational follow-up in conjunction with standard clinical care.
- For studies utilizing stored identifiable private information or identifiable biospecimens, researchers have the option of relying on "broad consent" in lieu of an informed consent for future unspecified (secondary) research.
- The establishment of new exempt categories of research based on the level of risk they pose to participants. For example, secondary research involving identifiable private information which is already protected by HIPAA (i.e. chart reviews involving recording of identifiable data) will be considered exempt.
- "Limited" IRB review of certain exempt research for the purpose of ensuring adequate confidentiality and privacy safeguards and/or broad consent
- Updated definitions and terms

The revised regulations will mean a variety of changes in IRB documents, policies and procedures. As changes are made within the IRB Office in response to the Final Rule, these will be communicated to the research community.

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Resources for more details: WIRB PowerPoint "Understanding the Final Common Rule": http://www.wcgclinical.com/wp-content/uploads/2017/01/WCG-Discussion-of-Common-Rule-Webinar-20jan2017.pdf Final Rule Resources developed by CITI Program: https://about.citiprogram.org/en/resources/ How the New Common Rule Will Impact Research in 2018 and Beyond: https://kinetiqideas.com/how-the-new-common-rule-will-impact-research-in-2018-and-beyond/ PRIM&R Revised Common Rule Page: https://www.primr.org/commonrule/

Ball Memorial Hospital

Published by the Department of Medical Research for physicians and staff at IU Health Ball Memorial Hospital.

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Extensive Small Cell Lung Cancer

Extensive Small Cell Lung Cancer "There Has Not Been a New Approved Therapy in 25 Years" IU Health Ball Memorial Cancer Center Research Team are Participating in a Clinical Trial with Hopes to See this Change.

The Indiana University Health Ball Memorial Hospital Cancer Center Medical Oncology Physicians and Research department are participating in a Phase III, Randomized, Multicenter, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination with Platinum-Based Chemotherapy for the First-Line Treatment in Patients with Extensive-Stage Small Cell Lung Cancer, the CASPIAN study. Dr. Joseph Spahr is the principal investigator for this exciting study. Our site received IU Health Ball Memorial Hospital Institutional Review Board approval for the study at the May 2017 meeting and our site initiation visit occurred on June 14, 2017. We enrolled our first patient at IU Health Ball Memorial Hospital on August 30, 2017; our patient is the fourth patient to be enrolled in the United States. The CASPIAN study has a planned enrollment of 795 patients worldwide.

There were approximately 225,000 new lung cancer cases diagnosed in 2016, of those diagnosed approximately 13% were Small-cell lung cancer. Small-cell lung cancer is strongly associated with tobacco smoking with equal diagnosis in men and women. Small-cell lung cancer is the most aggressive form of lung cancer and is known for its rapid growth and extremely high mutation rate. IU Health Ball Memorial had 21 diagnosed cases of Small-cell lung cancer in 2016. This exciting clinical trial is looking at adding immune therapy to standard of care chemotherapy versus standard of care chemotherapy for the treatment of extensive stage Small-cell lung cancer.

The trial is sponsored by AstraZeneca located in Sweden. The sponsor plans to have sites in the United States, Bulgaria, Czech Republic, Hungary, Israel, Italy, Netherlands, Poland, South Korea, Russia, Spain, Taiwan, Turkey and Ukraine. As of August 2017 the study has 124 active study sites, with 190 patients screened and 161 patients randomized to treatment.

Durvalumab is a human monoclonal antibody of the immunoglobulin G (IgG) 1 kapp subclass that blocks the interaction of PD-L1. Durvalumab acts to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. Durvalumab is an IV infusion that is given every three weeks times four along with the platinum based chemotherapy regimen and is supplied to patients at no cost.

Tremelimumab is a fully human IgG2 monoclonal antibody, which is directed against human cytotoxic T lymphocyte-associated antigen 4 (CTLA4), it is also an interleukin-2 (IL-2) stimulant. CTLA4 (CD152) is a cell surface receptor expressed on activated T cells. Tremelimumab is an IV infusion that is given every three weeks times four along with the platinum based chemotherapy regimen and is supplied to patients at no cost.

The trials primary objective is to assess the efficacy of durvalumab plus tremelimumab in combination with platinum based standard of care chemotherapy when compared to platinum based standard of care chemotherapy in terms of overall survival and progression free survival. The trial also has multiple planned secondary objectives.

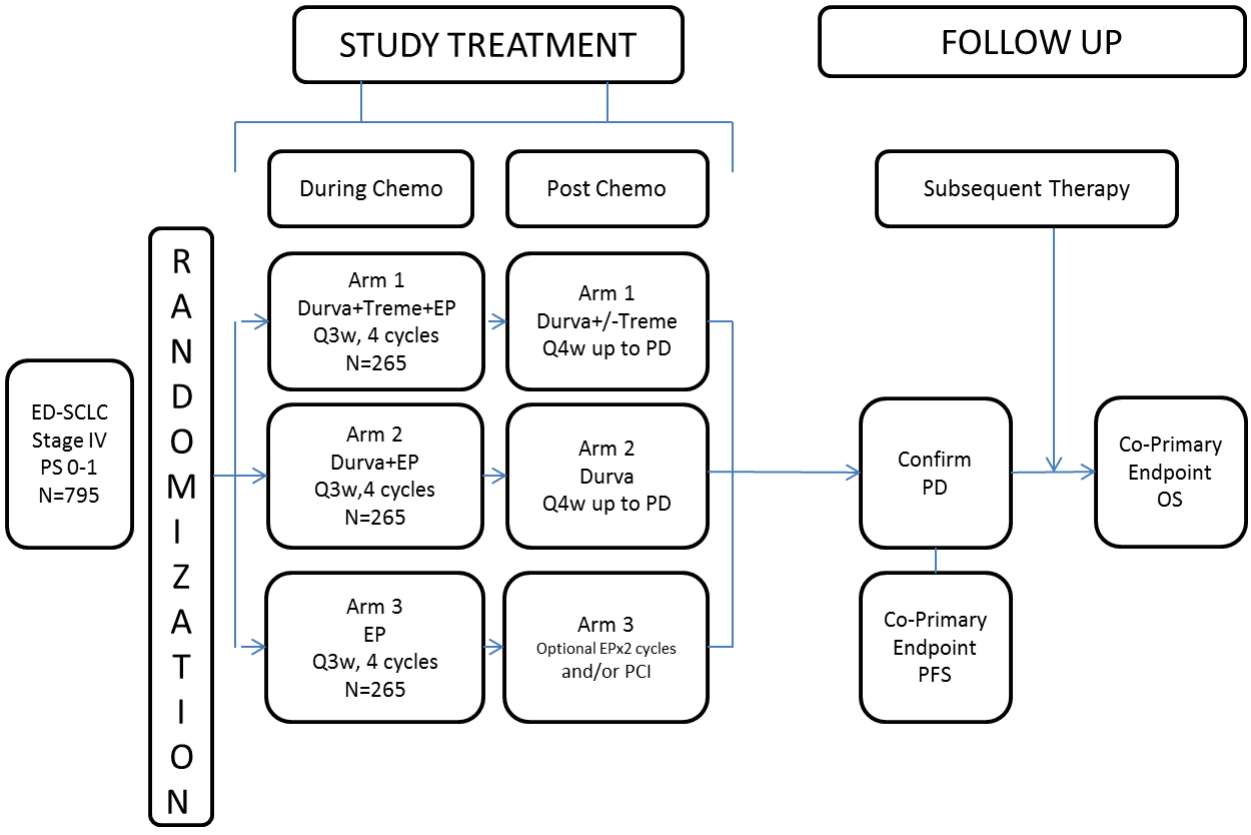
The currently known possible risks related to durvalumab and tremelimumab are:

- tiredness
- cough
- constipation/diarrhea
- abdominal pain
- numbness/pain in extremities
- dizziness
- insomnia
- skin changes/rash/itching
- feeling sick or being sick
- lung infection
- anorexia/loss of appetite
- sore mouth
- hypothyroidism
- headache
- nose bleed
- hypertension
- shortness of breath
- fever
- indigestion
- hearing changes
- edema/swelling in extremities
- anxiety
- hair loss
- blood clots
- pain, non-cardiac chest pain, pain in extremities, back pain, tumor pain

Key Inclusion Criteria Include:

- Patients suitable to receive 1st line platinum based chemotherapy
- Patients with a life expectancy of greater than 12 weeks
- Patients with adequate and bone marrow function
- Patients ECOG performance status of 0-1

Overall Study Design:



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Understanding Analysis of Variance (ANOVA)

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Previously we have discussed testing the difference between the means of two data sets (using continuous variables) using Student's t-test, and the differences between type I and type II errors. The t-test works fine when we are dealing with only two groups.

However, what if we want to work with three or more groups (common in biomedical studies)? Intuitively, it would seem natural to simply do several t-test comparisons—for four groups that would be six comparisons (A to B, A to C, A to D, B to C, B to D, C to D). For six groups you would have fifteen different two-group comparisons. (The number of two-group comparisons is N(N-1)/2).

So, aside from the extra work, what's the problem with doing six, fifteen, or even more comparisons of two means? The issue is that, in any statistical test, there is always a probability of making a Type I error (rejecting the null hypothesis or false positive—declaring a difference when there was no real effect) each time one does a comparison. This probability (alpha, ά) is typically set at 0.05 (5%) for most biomedical studies; we accept this small potential error as a "cost of doing business."

But this all breaks down when we apply the t-test to the same data repeatedly. If we, for example, do six different two-group comparisons, the probabilities are additive, leading to many problems with this type of approach. (The formula for determining the new error rate for multiple t-tests is not as simple as multiplying 5% by the number of tests (as it is somewhat less), but can easily exceed 25% for multiple groups, meaning one in four results is a false positive—not acceptable).

The answer to this dilemma: ANOVA (analysis of variance). ANOVA does not measure the differences between group means, but rather looks at how the entire collection of group means is distributed and compares them to the expected amount of distribution were all groups to be sampled from the same population.

There are three main assumptions for ANOVA to be valid:

1. The dependent variable is normally distributed in each group that is being compared;
2. There is homogeneity of variances. This means that the population variances in each group are equal;
3. Independence of observations.

We can perform one-way or two-way ANOVA. For the sake of brevity, I will only give an example of one-way ANOVA here as this is what is most commonly done. One-way ANOVA is used when there is only one factor of interest that could alter the result.

An example: we hypothesize there may be a correlation between 25-hydroxyvitamin D levels, osteopenia, and osteoporosis. You set up three different groups (according to bone density) and measure their 25-OH D levels (ng/mL):

Normal Bone Density	Osteopenia	Osteoporosis
54	32	19
43	40	22
57	31	27
49	27	17
50	24	29
52	33	30
49	34	22

We need to set up our hypotheses and determine the level of significance:

H_0: $\mu_1 = \mu_2 = \mu_3$; H_1: at least one mean is unequal; $\acute{\alpha} = 0.05$

For ANOVA we will want to calculate the F statistic (easily done in Excel or any commonly used statistical program).

F statistic	56.283
F, critical	3.555
Number of groups (e.g. columns)	3
p value	< 0.0001
Column means significantly different (p<0.05)	Yes
Significance level	95%

These results only tell us that there is at least one difference in the column means. Often, however, we want to know the differences between each column (three comparisons in a three-column test). There are a variety of post-comparison (post-hoc) tests; one commonly used test for parametric data is the Tukey test (Tukey range test, Tukey-Kramer test).

For three groups, we will have a total of (3)(3-1)/2 = 6/2 = 3 comparisons. Running the Tukey test on these data reveals a $p < 0.05$ for each comparison (A-B; B-C; A-C), revealing that all three groups differ significantly from one another.

Because post-comparison tests are run to confirm where the differences occurred between groups, they should only be done when we find an overall statistically significant difference in group means (i.e., a statistically significant one-way ANOVA result).

ANOVA can be done on much larger groups as well. This example is a one-way ANOVA as there is only one studied variable (vitamin D level) that can affect the result (bone density). We could set up a two-way ANOVA if we had a second variable (e.g., daily calcium intake) that could affect the result.

ANOVA and the associated post-comparison tests are useful tools in detecting the differences in the means of three or more unrelated groups, and avoids the statistical pitfalls of doing repeated Student's t-tests on each group.

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Approved Research Projects

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From January 1, 2017 through June 31, 2017, the following research projects and their principal investigators (PI) have been approved:

CAMELLIA: APD356-G000-401: A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Effect of Long-term Treatment with BELVIQ (lorcaserin HCl) on the Incidence of Major Adverse Cardiovascular Events and Conversion to Type 2 Diabetes Mellitus in Obese and Overweight Subjects with Cardiovascular Disease or Multiple Cardiovascular Risk Factors
PI: Bruce Graham, MD

LUN15-233 Randomized Phase II Trial of Docetaxel plus Nivolumab or Docetaxel alone in patients with advanced non-squamous NSCLC previously treated with single agent Nivolumab
PI: William Fisher, MD

GALACTIC-HF: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects With Chronic Heart Failure With Reduced Ejection Fraction (phase 3) AMG 423 20110203
PI: Wayne Gray, MD

PARADISE: A multi-center, randomized, double-blind, active-controlled, parallel-group Phase 3 study to evaluate the efficacy and safety of LCZ696 compared to ramipril on morbidity and mortality in high risk patients following an acute myocardial infarction
PI: Bruce Graham, MD

APPRAISE: Assessment of Primary Prevention Patients Receiving An ICD – Systematic Evaluation of ATP
PI: Bruce Graham, MD

HEART-FID: A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Injectafer® (Ferric Carboxymaltose) as Treatment for Heart Failure with Iron Deficiency
PI: Wayne Gray, MD

CASPIAN: A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment in Patients with Extensive Disease (Stage IV) Small-Cell Lung Cancer (SCLC)
PI: Joseph Spahr, MD

CONNECT-HF: CLCZ696BUS05T Care OptimizatioN through PatieNt and hospital Engagement Clinical Trial for Heart Failure
PI: Wayne Gray, MD

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Electronic Health Records: Can their uses facilitate clinical research?

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Electronic Health Records (EHR), originally designed to improve billing compliance, has streamlined patient care and generated performance measures within our clinical practice. Using EHRs within the scope of clinical research is currently being explored to facilitate improved research outcomes and performance. Clinical research has many challenges in which incorporating the capabilities of an EHR system could address: feasibility of a study; recruitment challenges; and data collection obstacles.

Determining whether a clinical research study is feasible at one's institution can be challenging. Due to limited resources, healthcare providers must be selective in what clinical trials to choose for their site and patient population. Statistics play a large role in determining the feasibility of a study. This is where data collected through an EHR can come into play. Through an EHR, patient demographics, vital statistics, and clinical aspects can be utilized to provide a concrete need for a proposed study. While registries provide statistics for a specific population, an EHR provides information for the entire clinical population within the healthcare entity's service area. In other words, statistics gathered through an EHR may provide a researcher with a more complete picture of whether a study would be feasible at their site.

Once a researcher determines a study is feasible at their site, the challenge of recruiting subjects must be considered. EHRs can be instrumental in identifying potential study patients. Screening rules, such as age, diagnosis, and specific exclusion criteria can be built into a system in order to generate a list of potential research patients. By generating this list through the EHR, the burden of identifying research patients could be potentially decreased. Keeping in mind that the screening rules are only as good as the rules themselves and the data entered into the EHR, complete or incomplete as it may be.

Lastly, EHRs have the potential to assist researchers in improved data collection. According to the Code of Federal Regulations 21 Part 11, electronic records and signatures are "trustworthy, reliable, and generally equivalent to paper records." Keeping this in mind, transcription errors can be significantly reduced if data from an EHR, such as concomitant medications, co-morbidities, and patient demographics are utilized as opposed to information copied onto a Case Report Form (CRF). Additionally, since EHRs are many times used to provide source data verification to both paper and electronic CRFs, incorporating EHR information may decrease the redundancy of entering data twice. EHRs can also be used to increase patient safety during a clinical trial. Prompt reporting of a serious adverse event (SAE) involving a patient can have an impact on both the patient themselves and the entire study. EHR systems have the capability of alerting providers that a patient has entered their healthcare entity. This can assist researchers to investigate any potential adverse event. Unfortunately, data collection through an EHR does not come without its own barriers. Patients may have more than one provider with each provider having their own independent EHR that does not link to one other. In this case, a complete capture of patient data cannot be obtained. In addition, the quality, reliability, and validity of data may not be the same across separate systems that may be fortunate enough to be linked.

Through the use of EHRs, clinical researchers may be able to overcome many of the challenges that encompass clinical trials management today. Determining the feasibility of a research study has the potential to become less burdensome through the use of an EHR system. Discovering innovative ways to utilize an EHR to recruit study patients should be looked into further in order to improve subject participation in clinical research. Lastly, many obstacles in research data collection may be overcome by discovering new innovations in the use of an EHR as it pertains to clinical research.

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IU Health Ball Memorial Hospital
Research News
is published by the
Department of Research
for physicians and staff.
Information to be included
in this publication may
be sent to:
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