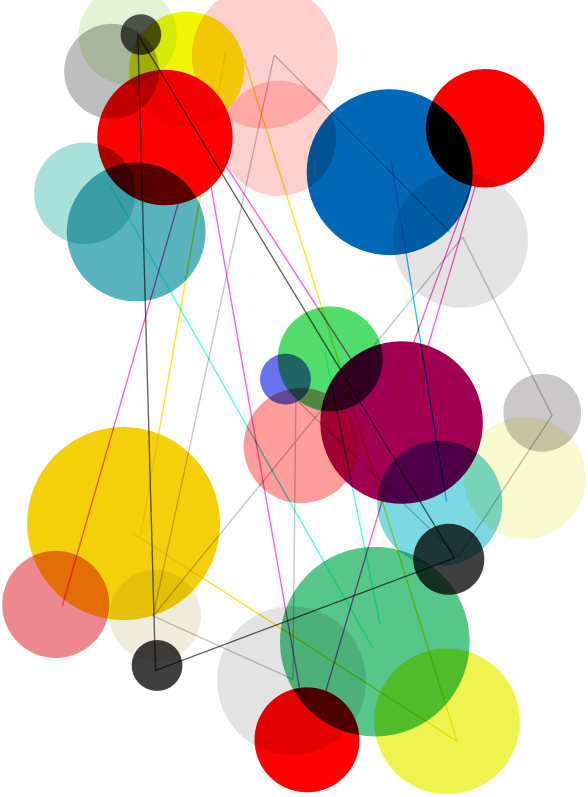

EthicsLab Context Booklet

for the Preeclampsia-Cleviprex project.

VERSION 1 – DRAFT

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Introduction

This document serves to capture some of the relevant context for the beginning of the EthicsLab + The Medicines Company (MDCO) collaboration on the Preeclampsia-Cleviprex project. This is the first (rough) draft, prepared ahead of the first sessions with MDCO at EthicsLab on April 21st and 22nd, 2014.

The organization of topics and the content within each section is preliminary. Furthermore, all of the content within this booklet has been prepared solely by EthicsLab designers and has not been proofed by any of the experts involved (i.e., neither MDCO nor EthicsLab bioethicists have reviewed this version upon printing). This method of using a booklet for context research and capture is also experimental—something we are testing as we build and institutionalize EthicsLab processes and practices.

Our intentions for this initial draft are:

1. To provide context and reference that can be accessed *in situ* during our first sessions on this project;
2. To collect feedback from participants on the content during and after the session so that we may improve it for future use and publication;
3. To explore and collect feedback on the use of a context booklet in the EthicsLab design process.

- The EthicsLab design team

April 20th, 2014

Preeclampsia

Preeclampsia is a multi-system disorder characterized by hypertension and proteinuria occurring after the twentieth week of pregnancy in a woman who previously had normal blood pressure. Swelling, sudden weight gain, headaches and changes in vision are the primary symptoms; however, some women with rapidly advancing disease report few symptoms. Preeclampsia can lead to eclampsia when there is hypertension and seizure. Currently, the only cure for preeclampsia is delivery of the fetus.[1] Preeclampsia is estimated to affect 5-8% of all pregnancies.

Cause

Although preeclampsia has been recognized for many years, its etiology is not fully understood. We know that the hypertension is caused by placental invasion of underlying blood vessels that cause high blood pressure, but the mechanism by which this occurs is not clear. This type of hypertension, eclamptic hypertension, is physiologically different than the much more common (but also ill-understood) essential hypertension.

Diagnosis

Every patient is unique, but there are commonly two factors in the diagnosis of preeclampsia: hypertension and proteinuria (protein in the urine). In this context, hypertension is defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on two occasions at least 4 hours apart for 20 weeks of gestation in a previously normotensive patient, or if systolic blood pressure is ≥ 160 mmHg or diastolic blood pressure is ≥ 110 mmHg, confirmation within minutes is sufficient. Paired with the blood pressure measurements

above, proteinuria ≥ 0.3 grams in a 24-hour urine specimen or protein (mg/dL)/creatine (mg/dL) ratio ≥ 0.3 is considered diagnostic of preeclampsia.

Treatment

The pharmacological interventions used to treat preeclampsia are calcium channel blockers. This class of drug works as a smooth muscle relaxant. Smooth muscle lines the vessels of the arteries that cause the high blood pressure. The same drugs function as anticonvulsants because they block the receptor in the brain that contributes to seizures. Magnesium sulfate is the most common intervention to treat hypertension and seizures in pregnant women, but other drugs such as labetalol (a beta blocker) or hydralazine may be used. Drugs are generally chosen based on provider preference and patient clinical scenario. For example, labetalol cannot be used if the patient has a low heart rate, and hydralazine cannot be used if the patient has lupus.

When a pregnant woman is diagnosed with hypertension before 34–36 weeks into her pregnancy, she is generally sent home and put on bed rest until the fetus reaches term. If the woman is 36 weeks into her pregnancy or showing signs of severe preeclampsia, she is admitted to the hospital for blood pressure control and subsequent induction of labor. Admission to the hospital includes serial blood pressure monitoring, steroids administered to the mother that help the baby's lungs mature before delivery, and the baby's heart rate is constantly monitored. If required, blood pressure control is administered intravenously. Doses for blood pressure control drugs are usually set initially and then titrated (changing the doses based on how the blood pressure is responding). A fetal ultrasound is also done to further assure no fetal distress. Induction may be done with intravenous medication or intravaginal medication.

It should be noted that all hypertension in pregnancy is not preeclampsia. Underlying hypertension may be present before gestation.

Cleviprex

Cleviprex (clevidipine) is a dihydropyridine L-type (long-lasting) calcium channel blocker developed by The Medicines Company. L-type calcium channels mediate the influx of calcium during depolarization in arterial smooth muscle. Depolarization means that the entry of calcium causes smooth muscle cell contraction, which when unregulated, causes hypertension. So, blocking the calcium channels, as Cleviprex does, will lower blood pressure.

Intended Use

Cleviprex is intended for intravenous use in acute care settings (emergency rooms, intensive care units, before and after major surgery) when oral therapy is not feasible or not desirable.

Use In Pregnant Women

Cleviprex is currently classified as Pregnancy Category C by the FDA. This categorization indicates that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. In animal studies, Cleviprex caused increases in maternal and fetal mortality and length of gestation. Cleviprex has been shown to cross the placental membrane in rats.

Clinical Trials

When bringing a new medical intervention to market, research is required to test the safety and efficacy of the new treatment. Research is defined by the Department of Health and Human Services as a "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."[2] In this booklet, we focus on clinical trials with human subjects. Federal regulations define a human subject as "a living individual about whom an investigator (whether professional or student) conducting research obtains: 1) Data through intervention or interaction with the individual, or 2) Identifiable private information."[2] There are obviously ethical concerns when testing a new drug or other medical treatment on humans because its effects are by definition unknown. This inherent risk leads investigators to design trials in phases aimed at mitigating that risk.

Types of Clinical Trials

We may divide clinical trials into four major types[3]. In practice, a single may combine or overlap these types across different phases.

Human pharmacology studies typically assess tolerance, define PK (pharmacokinetics, the body's effect on a drug) and PD (pharmacodynamics, a drug's effect on the body), explore drug metabolism and drug interactions, and estimate activity. These studies may be described as "first in human" studies and are usually conducted in healthy patients to test the safety of a compound at increasing dosage levels to establish a maximum safe dose.

Therapeutic exploratory studies explore use for the targeted indication, estimate dosage for subsequent studies, and provide a basis for confirmatory study design, endpoints, and methodologies. Trials of this type may include

earliest trials of relatively short duration in well-defined narrow patient populations; trials using surrogate (laboratory measurement or physical sign used as a substitute for clinical endpoint), pharmacological endpoints, or clinical measures; and dose-response exploration studies.

Therapeutic confirmatory studies demonstrate or confirm efficacy, establish safety profile, provide an adequate basis for assessing the benefit-risk relationship to support licensing, and establish the dose-response relationship. These trials include adequate, and well-controlled studies to establish efficacy; randomized parallel dose-response studies; clinical safety studies; studies of mortality and morbidity outcomes; large simple trials; comparative studies.

Therapeutic use studies refine understanding of the benefit-risk relationship in general or special populations and/or environments, identify less common adverse reactions, and refine the dosing recommendation. These studies may include comparative effectiveness studies, studies of mortality and morbidity outcomes, studies of additional endpoints, large simple trials, and pharmacoeconomic studies that evaluate the cost (expressed in monetary terms) and effects (expressed in terms of monetary value, efficacy or enhanced quality of life) intended to guide optimal healthcare resource allocation, in a standardized and scientifically grounded manner.

Institutional Review Boards (IRBs)

Before any trial in the United States can begin, it must be approved by an Institutional Review Board (IRB). These bodies are the gatekeepers between investigators and patients, and their role is primarily to protect patient safety. IRBs review and approve all research involving human subjects at their home institutions, with an eye toward scientific validity and ethical acceptability.

The typical criteria for IRB approval are[4]:

1. The risks to subjects are minimized as much as possible;
2. The risks to subjects are reasonable in relation to anticipated benefits;
3. The informed consent is adequate;
4. Where appropriate, the research plan makes provisions for the safety of the subjects during the data collection process;
5. Where appropriate, there are adequate provisions to protect the privacy of subjects and maintain confidentiality of data;
6. Appropriate safeguards are included within the study to protect the rights and welfare of the vulnerable subjects.

IRBs and Research With Pregnant Women

Given the added complexity and ethical concerns inherent to research involving pregnant women, there are additional considerations for the approval of clinical trials in that context. Blehar et al. (2013) address the relationship between IRBs and clinical trials with pregnant women[5]:

> There are several factors leading to reluctance to include pregnant women in clinical research. Researchers are sometimes concerned about the physiologic complexity in pregnancy, and possible legal liability. Existing regulations governing the inclusion of pregnant women in clinical research are somewhat ambiguous, imposing another significant barrier to their implementation. Additionally, IRBs may go beyond regulatory requirements when the proposed subjects are pregnant women. Although not specific to pregnancy research, variation among IRBs in the interpretation of regulations for the same protocol is a further impediment, especially in multisite studies.

Problems have been identified with IRB interpretation of regulations governing clinical research that includes pregnant women as subjects (Levine, 2011). As an example, wording in Subpart B states that pregnant women or fetuses may be involved in research if all of ten enumerated conditions are met. Condition (a) specifies that research may be conducted where scientifically appropriate, preclinical and clinical studies on nonpregnant women provide an adequate basis for assessing potential risks to pregnant women and fetuses. IRBs are left to interpret how much prior research is sufficient and they typically interpret this directive conservatively.

The interpretation of "minimal risk to the fetus" in condition (d) of Subpart B is particularly problematic. Despite clarifications in 2005 by the Secretary's Advisory Committee on Human Subjects Research, as well as clarifications from the IOM and other organizations, arguments continue about the meaning of minimal risk and interpretations vary widely.

Testing of drug therapies in a pediatric population presents an analogous situation to testing of drugs in a pregnant population. Several studies reveal inconsistencies among IRBs in applying regulations governing clinical research to studies involving children (Whittle et al., 2004; Kimberly et al., 2006). A survey (Shah et al., 2004) asked IRB chairs to evaluate the degree of risk for various kinds of research on children. For a study in children testing a drug already found safe in adults, only five percent of IRB chairs said that the study presented minimal risk and 72 percent felt that this was greater than a minor increase above minimal risk. Even for a pharmacokinetic study, in which the risk of death is estimated to be less than one in a million, 53 percent of IRB chairs evaluated it as greater than a minor increase over minimal risk.

Although IRB inconsistency is likely due in large part to differences in interpreting regulatory requirements and ethical standards, it might also stem from some IRB members' lack of necessary expertise regarding re-

search ethics and regulations for research with special populations of children or pregnant women. Specialized committees as well as training of IRB members in the specific requirements of regulations for such populations may be helpful.

A July 2011 Federal Register Announcement sought input on possible changes to the Common Rule and to Federal Regulations 21 CFR Parts 50 and 56 Human Subjects in order to enhance protections for research subjects and reduce burden, delay, and ambiguity for investigators. The announcement noted that regulations have not kept pace with the evolving human research enterprise, the proliferation of multi-site clinical trials and observational studies, the expansion of health services research, research in the social and behavioral sciences, and research involving databases, the Internet, and biological specimens in repositories, and the use of advanced technologies, such as genomics.

Proposed revisions included those to reduce impediments to IRB approval for multisite protocols. Although the changes discussed did not specifically address regulatory-defined "vulnerable" populations such as pregnant women, it was noted that regulations for these populations will likely be affected by changes and will need to be harmonized, as appropriate, with any changes made to the Common Rule.

Physiological Intricacy of Pregnancy

Lyerly and Faden (2013) discuss the additional physiological intricacy of pharmacokinetics and pharmacodynamics in pregnant women[6]:

> This can be a serious problem because pregnancy often changes the ways that drugs act in the body—the drug's pharmacokinetics and pharmacodynamics. Several recent studies have shown that using standard adult

doses of drugs or vaccines in pregnant women can lead to undertreatment or overtreatment. For instance, in the wake of rates of morbidity and mortality among pregnant women that exceeded that of the general population in the recent H1N1 pandemic [3], researchers investigated the pharmacokinetics of the drug oseltmavir phosphate (Tamiflu) in pregnant women and found that the standard adult dose (which was recommended for pregnant women during the pandemic) may be inadequate for treatment or prevention of flu during pregnancy [4].

Further, there are few data to address worries about fetal safety. For 98 percent of the drugs approved between 2000 and 2010, the teratogenic risk is unknown [5]; for drugs approved in the previous 20 years, we still don't know enough about nearly 9 out of 10 [5]. The average time it takes for a drug to be categorized in terms of risk is 27 years after market approval [5].

In the absence of clear data about the appropriate dosing or safety of medications, women (and their doctors) are often reticent to use (or prescribe) drugs during pregnancy. But excess precaution has serious downsides. Specifically, untreated illness can present far greater risks than those posed by medications. Untreated asthma is associated with preeclampsia, premature delivery, low birth weight, and hemorrhage, but women whose asthma is controlled have outcomes comparable to women without asthma [6]. Treatment delays possibly attributable to reticence had serious consequences for pregnant women during the H1N1 pandemic: women who received treatment more than 4 days after the onset of symptoms were more likely to be admitted to the intensive care unit and receive mechanical ventilation—and more than 50 times as likely to die—than women who received timely treatment with antivirals [7].

How should we redress this state of affairs? Perhaps the most important lesson is that we can no longer hide behind claims that ethics precludes the inclusion of pregnant women and their interests in research. Rather,

ethics—and to be more precise, justice—demands that we move forward with their responsible inclusion. Pregnant women have not benefitted fairly from the research enterprise. It is well past time that they do.

The first step is recognizing that there are many ways to gather data without having to sort out the ethical complexities of risk trade-offs between pregnant women and their fetuses. There is plenty of what might be called ethical low-hanging fruit—ethically unproblematic research that can help fill the evidence gap about health care for pregnant women. For instance, a wealth of critical information about the pharmacokinetics of drugs in pregnancy could be garnered by doing a simple series of blood tests on pregnant women who are already taking medications. The National Institutes of Health's Obstetric-Fetal Pharmacology Research Units have funded several such "opportunistic" studies in the last several years [8], yet major gaps remain. For instance, HIV-related tuberculosis accounts for 10 percent of maternal deaths in some developing countries [9], yet there are no pharmacokinetic data on any TB medications and, of the 40 TB trials currently underway, all exclude pregnant women [10].

In addition to opportunistic pharmacokinetic studies, large cohort trials can be a rich source of information, but these golden opportunities are—all too often—overlooked. For instance, in 2009 the NIH launched the National Children's Study; more than 100,000 women were to be followed during pregnancy and their children would be followed for 20 years to understand the impact of the environment on children's health. The problem is that pregnant women—consenting research participants—were understood not as subjects but as part of the environment to be studied, as the data collected pertained almost exclusively to children's health [11].

Studies that involve more than minimal risks to fetuses tend to raise red flags among researchers, IRBs, and even patients themselves. It is important to remember, however, that participation in a research study—in which there are rigorous standards for informed consent and close moni-

toring—may well be a safer context for the use of medications in pregnancy than the clinical setting, where the evidence base is so profoundly lacking. In considering the ethics of trial participation, we cannot forget context: if women are excluded from research, their only option may be to take a medication in an uncontrolled clinical environment absent the data to inform dosing or safety considerations specific to pregnancy. Absent systematic research involving pregnant women, their only option will remain having their illnesses treated in this uncontrolled clinical environment in which the data needed to secure FDA approval remains elusive. Indeed, the American College of Obstetricians and Gynecologists endorsed—for nearly a decade before FDA approval—the use of the medications in Diclegis in pregnant women suffering from NVP [12].

Though approval by the FDA, and a pregnancy category A to boot [13], are both reassuring—and in the case of Diclegis, long-awaited by the many women who did take the drug years ago—what we need most are data, so that women can make informed decisions about whether or not to use a medication during pregnancy and so that doctors can prescribe such medicines at appropriate and effective doses. Still, with the FDA's recent decision, it feels like a page has turned in the history of maternal health. Let's hope the momentum continues.

Regulations

In the United States, pharmaceuticals are regulated by the Food and Drug Administration (FDA): a science-based regulatory and public health agency charged with assuring the safety, efficacy, and security of medical products. The core function of the FDA is to protect patients by applying the "best possible science to its regulatory activities." To that end, the FDA is responsible for advancing public health not only by helping to speed innovations that make medicines safer and more effective, but also by helping patients and health care professionals get the information they need to make appropriate decisions about the use of a particular medicine.

In Europe, each member state has in place a regulatory agency with mandate similar to that of the FDA—for instance, the Medicines and Healthcare Products Regulatory Association (MHRA) in the UK, the Federal Institute for Drugs and Medical Devices (BfArM) in Germany, the newly-created National Agency for the Safety of Medicines and Health Products (MSNA) in France, and the Italian Medicines Agency (AIFA) in Italy. In addition, each member state also has local regulatory systems that are often run in full collaboration with the pharmaceutical industry (such as the Association of the British Pharmaceutical Industry [ABPI] in the UK) and are responsible for the oversight and maintenance of high-quality ethical, legal, scientific, and promotional standards by the pharmaceutical industry.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating across Europe and provides a set of quality standards and guidelines for pharmaceutical promotion and how these are applied across member states.[7]

Relevant FDA Regulations

[from US Code of Federal Regulations (CFR), Title 21: Food and Drugs, Part 50: Protection of Human Subjects]

§50.20 General requirements for informed consent.

Except as provided in 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

§50.23 Exception from general requirements.

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

> (1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.
>
> (2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

[...Truncated (d) – (e)]

§50.24 Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will

summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

§50.25 Elements of informed consent. [Also 45 CFR 46.116, HHS]

(a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(c) When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section

402 of the Public Health Service Act. The statement is: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

(d) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(e) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

§50.27 Documentation of informed consent. [Also 45 CFR 46.117, HHS]

(a) Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

(b) Except as provided in 56.109(c), the consent form may be either of the following:

> (1) A written consent document that embodies the elements of informed consent required by 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.
>
> (2) A short form written consent document stating that the elements of informed consent required by 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a

copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

Relevant HHS Regulations

[from Code of Federal Regulations (CFR), Title 45: Public Welfare, Part 46: Protection of Human Subjects]

§46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cogni-

zant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§46.204 Research involving pregnant women or fetuses.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

Bioethics

A number of ethical concerns cut across the context of this project. This section outlines some of these concerns, without any pretense of being comprehensive.

Autonomy

Autonomy is defined as an individual's capacity for self-determination. Autonomous agents act with intention, understanding, and freedom from controlling influences. Respect for autonomy is a fundamental ethical obligation in clinical research and practice. This involves more than allowing patients to make their own decisions—clinicians have an obligation to prepare, inform, and create the conditions for patients to exercise their autonomy in decisions.[8]

Legally, a pregnant woman cannot be compelled to undergo a medical intervention even when the fetus' survival depends on it. Questions exist about whether and in what ways a pregnant woman takes on special duties to protect her future child if she decides to continue the pregnancy. However, whatever duties may or may not exist are separate from a woman's right to autonomy.[9]

Informed consent

Consent to a medical intervention is considered fully informed when a competent patient or research subject, to whom full disclosures have been made with full understanding, voluntarily consents to treatment or participation on this basis. Bioethical consensus holds that when a competent adult does not give sufficiently informed and voluntary consent to a medical intervention, then the intervention is impermissible—even when it seeks to assist her, even when physicians recommend it, even if third parties would benefit from it, and even

where the patient herself had repeatedly consented to it before expressing a change of mind.

Real-world consent is triply complicated by the difficulty of establishing each of the three crucial ingredients of informed consent: that consent is [1] freely given and [2] fully informed, and that [3] the consenter is truly competent.[10] Ordinary epistemic difficulties in establishing that [1]–[3] are met are compounded in emergency or acute care settings, when time is scarce and patients are extremely unwell; in novel experimental contexts, when full information may be hard to obtain or communicate; and in surrogate or proxy situations in which one or more parties affected by the medical intervention are entirely incapable of consenting to it.

Beneficence

Beneficent action is performed for the benefit of others. The goal of medicine is to promote the welfare of patients, and physicians and clinician-investigators possess skills and knowledge that enable them to assist others. According to many ethicists, these skills entail an obligation to [1] prevent and remove harms, and [2] weigh and balance possible benefits against possible risks of an action, for patients or research subjects who stand to be benefitted by the action and choices of the skilled practitioner.[11]

Nonmaleficence

The principle of nonmaleficence requires that we not intentionally harm another, whether through acts of commission or omission. This principle affirms the need for medical competence. In addition to not doing anything that would purposely harm patients or research subjects (without corresponding and commensurate expected benefit), nonmaleficence requires that physicians or clinical investigators refrain from providing ineffective treatments, or those that offer risk with little or no possibility of benefit.[12]

Justice

The principle of justice is linked to fairness, entitlement and equality. In biomedical ethics, this can be subdivided into three categories: fair distribution of scarce resources (distributive justice), respect for people's rights (rights based justice) and respect for morally acceptable laws (legal justice).[13] At its heart, the principle of justice requires fair treatment and equality of access to health care resources, including medical knowledge.[14]

Clinical Equipoise

Coined by Benjamin Freedman in 1987, the term "clinical equipoise" refers to a state of genuine uncertainty on the part of a clinical investigator regarding the comparative therapeutic merits of each arm in a trial.[15] The principle of equipoise states that this condition of uncertainty is a prerequisite for ethical research: should an investigator discover that one treatment is of superior therapeutic merit, she is morally obliged to offer that treatment.

There are different ways of interpreting the principle of equipoise, from the stringent requirement that each individual investigator have no "treatment preference" throughout the course of any trial in which she is involved, to the more relaxed interpretation according to which the requirement is satisfied if there is genuine uncertainty within the expert medical community—not necessarily on the part of the individual investigator—about the preferred treatment.[16]

International Ethical Guidance

The Nuremberg Code

1. The voluntary consent of the human subject is absolutely essential.

   This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment.

   The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted, where there is an apriori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end, if he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.

10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Other Documents

- CIOMS Guidelines for Biomedical Research Involving Human Subjects
- CIOMS Guidelines for Ethical Review of Epidemiological Studies
- WHO: Guidelines for Good Clinical Practice
- World Medical Association (WMA): Declaration of Helsinki
- UN's International Covenant on Civil and Political Rights
- EU Directive

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[3] Adapted from "Table 1.—An Approach To Classifying Clinical Studies According To Objective" of "International Conference on Harmonisation; Guidance on General Considerations for Clinical Trials," *Federal Register* 17, December 1997, 62 (242): 66115.

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[16] Cook, Charles, and Charles Sheets. "Clinical equipoise and personal equipoise: two necessary ingredients for reducing bias in manual therapy trials." *Journal of Manual & Manipulative Therapy*, Feb 2011; 19 (1): 55–57.

GEORGETOWN UNIVERSITY

EthicsLab
Healy Hall, 201b
Georgetown University
37th and O Streets, NW
Washington, DC 20057