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# CTMC 2022 Webinar Series: Ethical Issues in Acute and Chronic Neurological Conditions

1. Review ethical principles for human subjects research
2. Discuss issues related to post trial access to implanted neural devices
3. Discuss EFIC requirements and enrollment of conscious patients

SPECIAL ARTICLE

# AAN position statement: Ethical issues in clinical research in neurology

Benjamin Tolchin, MD, MS,\* Robin Conwit, MD,\* Leon G. Epstein, MD, and James A. Russell, DO, MS, on behalf of the Ethics, Law, and Humanities Committee, a joint committee of the American Academy of Neurology, American Neurological Association, and Child Neurology Society

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- This update to the American Academy of Neurology's 1998 position statement endeavors to provide guidance for the consistent ethical conduct and review of neurologic research involving human participants.

## Special Communication

May 24/31, 2000

# What Makes Clinical Research Ethical?

Ezekiel J. Emanuel, MD, PhD; David Wendler, PhD; Christine Grady, PhD

### Author Affiliations

JAMA. 2000;283(20):2701-2711. doi:10.1001/jama.283.20.2701

- *...framework of 7 principles for the ethical analysis of research on human Participants*
  - *For the purposes of this position statement, we will make use of these 7 principles as a practical and concise*
  - *distillation of the fundamental ethical guidelines detailed at greater length in the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, and the Common Rule.*
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# 7 principles for the ethical analysis of research on human participants

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**Table** Ethical principles for clinical research

Requirement	Summary	Examples of violations
<b>Social value</b>	A study must have the potential to improve human health or meaningfully increase society's knowledge of human biology	A placebo-controlled trial of a "me-too" medication, i.e., no safer, more effective, or cheaper than existing medications for the same illness

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<b>Respect for enrolled and potential participants</b>	Potential and enrolled participants must be treated respectfully, with attention to and protection of their privacy and interests throughout the course of the study	A study of a genetic test in which identifiable results can be obtained by employers, law enforcement, or others

The Belmont  
Report (1979)  
Ethical Principles  
and Guidelines for  
the Protection of  
Human Subjects of  
Research



“ To respect autonomy is to give weight to the autonomous person’s considered opinions and choices while refraining from obstructing his or her actions... ”

– Belmont Report

**Respect for Persons**  
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RESPECT FOR PERSONS

Four ethical research requirements follow directly from the principle of respect for persons:

1. Participants must voluntarily consent to participate in research.
2. The consent must be informed consent.
3. Participants’ privacy and confidentiality must be protected.
4. Participants have the right to withdraw from research participation without penalty or repercussions.

“ Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term beneficence is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. ”

**Beneficence**  
Beneficence  
Beneficence  
Beneficence

– Belmont Report

- The principle of beneficence requires that research be designed to maximize benefit and minimize harm.
  - the risks of the research must be justified by the potential benefits to the individual and/or society

“ Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects. ”

– Belmont Report

Justice  
Justice  
Justice  
Justice

- The concept of justice relates to the distribution of risk across society.
  - members of society who are likely to benefit from the research bear the potential risks of such research equally.
  - the research should not systematically select specific classes of individuals simply because they are readily available or because they are “easy to manipulate as a result of their illness or socioeconomic condition”
  - enrollment should focus on individuals for reasons directly related to the research
  - recent debate over whether the principle of justice also extends to protect persons from systematic exclusion from research that may apply to them

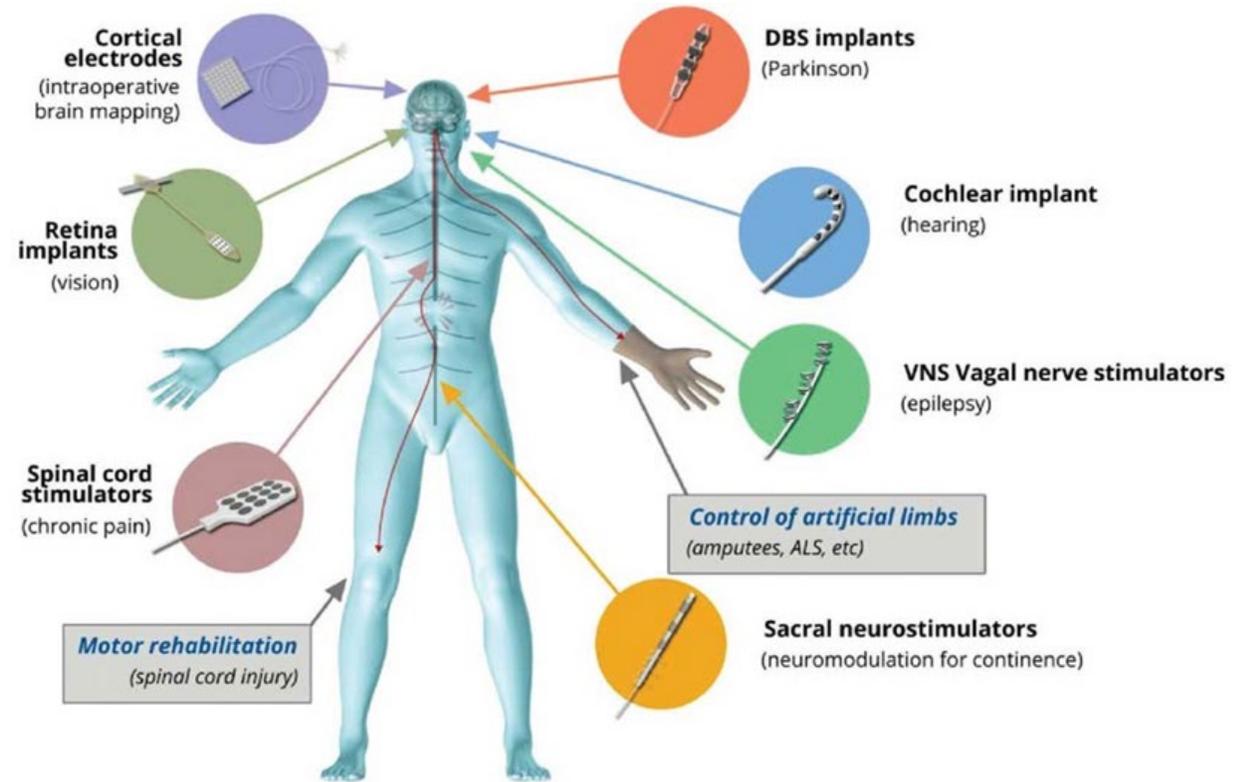
# WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

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1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

# Applying ethical principles in implanted neural device research

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# Proposed DBS study to improve gait in Stroke Patients

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- Based on PD DBS therapy
- *concern raised was that the DBS itself would work and we'd have to remove it from patients after the study as it's maintenance and programming wouldn't be covered by insurance.*
- Study was never initiated



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Contents lists available at ScienceDirect

## Brain Stimulation

journal homepage: <http://www.journals.elsevier.com/brain-stimulation>



### Post-trial access in implanted neural device research: Device maintenance, abandonment, and cost



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Kristin Kostick-Quenet <sup>d</sup>, Clarissa E. Sanchez <sup>d</sup>, Laura Torgerson <sup>d</sup>, Jill Robinson <sup>d</sup>,  
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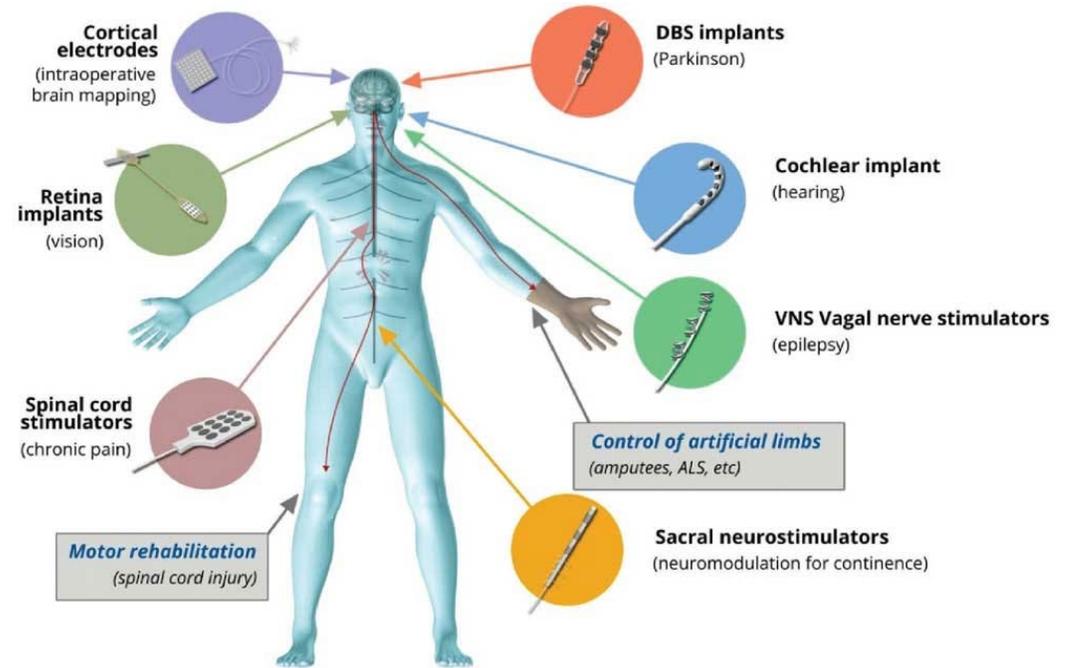
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# Background:

- Clinical trial participants who benefit from experimental neural devices for the treatment of debilitating and otherwise treatment-resistant conditions are generally not ensured continued access to effective therapy or maintenance of devices at the conclusion of trials.



# Do participants have a right to continued access?

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- AAN Position
  - Respect for participants?
- Belmont Report
  - Beneficence?
- DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS
  - 34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

# Do participants have a right to continued access?

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- most participants felt that they should be able to keep the device

# What are the barriers to continued access?

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- cost of maintenance
- regulatory restrictions as a barrier to continued access, mainly because the devices or indications are not FDA approved
- limited access to clinical and technical expertise

# Should researchers act as advocates for continued access?

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- reducing costs for participants by charging specialized visits as regular visits
- facilitating insurance coverage for participants
- choose sponsors that offer follow-up care
- running the trial at the VA
- applied for follow-up grants that include continued access costs in the budget

# How should the study team address continued access during the consent process?

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- Long-term implications of a lack of post-trial access
- Some participants do not recall any discussions about continued access
- “therapeutic misconception”?

# Which participants should be able to have continued access?

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- Those that benefit from the treatment
- What level of benefit?

# Who should pay for keeping the device functioning post-trial ?

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- Device manufacturers
- Insurance
- Participants
- Research teams

Exception from Informed Consent (EFIC)

Planned Emergency Research

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# EFIC Rules FDA and HHS

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- Planned Emergency Research subject to HHS regulations 45CFR46 may also be approved with and exception to informed consent per letter number 97-01 from OPRR dated Oct 31, 1996

Code of Federal Regulations]  
Title 21, Volume 1]  
Revised as of April 1, 2019]  
[CFR: 21CFR50.24]

TITLE 21--FOOD AND DRUGS  
CHAPTER I--FOOD AND DRUG ADMINISTRATION  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
SUBCHAPTER A--GENERAL

PART 50 -- PROTECTION OF HUMAN SUBJECTS

Part B--Informed Consent of Human Subjects

Sec. 50.24 Exception from informed consent requirements for emergency re

a) The IRB responsible for the review, approval, and continuing review of an investigation described in this section may approve that investigation without the 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 participating in the clinical investigation) finds and documents each of

# Conditions for study to be eligible for EFIC

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1. Life-threatening situation that necessitates urgent intervention
2. Available treatments are unproven or unsatisfactory
3. Collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention
4. Obtaining informed consent is not feasible
5. The intervention must be administered before consent can be obtained from the subject's legally authorized representative.
6. No reasonable way to prospectively identify potential participants
7. Participation holds out the prospect of direct benefit to the subjects
8. Could not practicably be carried out without the waiver

How to enroll patients that are  
conscious but unable to understand a  
full consent process under EFIC?



# Is it possible for an individual to indicate that he/she does not want to participate in an emergency research study?

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- The emergency situations to which 21 CFR 50.24 applies involve individuals who are typically unconscious or otherwise unable to communicate.
- There may be some cases in which an individual may be conscious and able to communicate. In such cases, while full consent may be difficult or impossible, an individual may be able to indicate that he/she does not want to participate in the emergency research study, prior to administration of the test article.
- If the individual declines to participate in the research, his/her wishes must be honored (21 CFR 50.20).

# Study Design

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- Therapeutic Window – 5 minutes

# Study Design

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- Patients eligible for this study will be conscious and may be able to communicate, however, due to their compromised capacity to make informed decisions, a full consent would be impossible.
- While full consent is impossible, the patient may still be able to indicate that they do not want to participate in the study, prior to administration of the test article.
- If the patient declines to participate in the research, his/her wishes will be honored.
- If the patient is unable to understand the opt-out script, the patient will not be enrolled.

# Opt-out process

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- eligible patients will be given a short description of the protocol by EMS personnel and will have the option of declining to participate.
- This process has been incorporated into the enrollment process as an additional protection of the rights and welfare of subjects

# LAR and NOK requirements

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- 21 CFR 50.24 (a)(5) ...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.
- 21 CFR 50.24(a)(7) Additional protections of the rights and welfare of subjects will be provided, including, at least: ... (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.**

# 21 CFR 50.24 (a)(5) -reponse

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- The narrow therapeutic window described above, the inability of patients to provide informed consent, and the lack of an LAR being reasonably available in the prehospital setting to provide surrogate consent, precludes the possibility of obtaining informed consent for eligible patients.

# 21 CFR 50.24(a)(7) - response

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- Since patients will not be enrolled in the study if they decline participation and will also not be enrolled if they do not understand the opt out script, it is not feasible to ask a family member if they object to a patient's enrollment in the study.
- The choice to participate will have already been made by the patient. If they are not capable of making this choice, they will not be enrolled.
- Contacting a family member of a patient to ask them if they object to the patient being in the clinical investigation is not feasible would not add any additional protection of the rights and welfare of subjects.
- If a family member is readily available, they would be included in the opt-out discussion with the patient.

# FDA Response

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- We acknowledge your statement that “It is not feasible to obtain consent from the subjects’ legally authorized representative within this narrow therapeutic window” and agree that in most, if not all cases, this may be true. However,
- as required by 21 CFR 50.24(a)(5) you must commit 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.”
- as required by 21 CFR 50.25(a)(7)(v) you must commit to reach out to family members to determine “whether he or she objects to the subject’s participation” in the clinical investigation when feasible

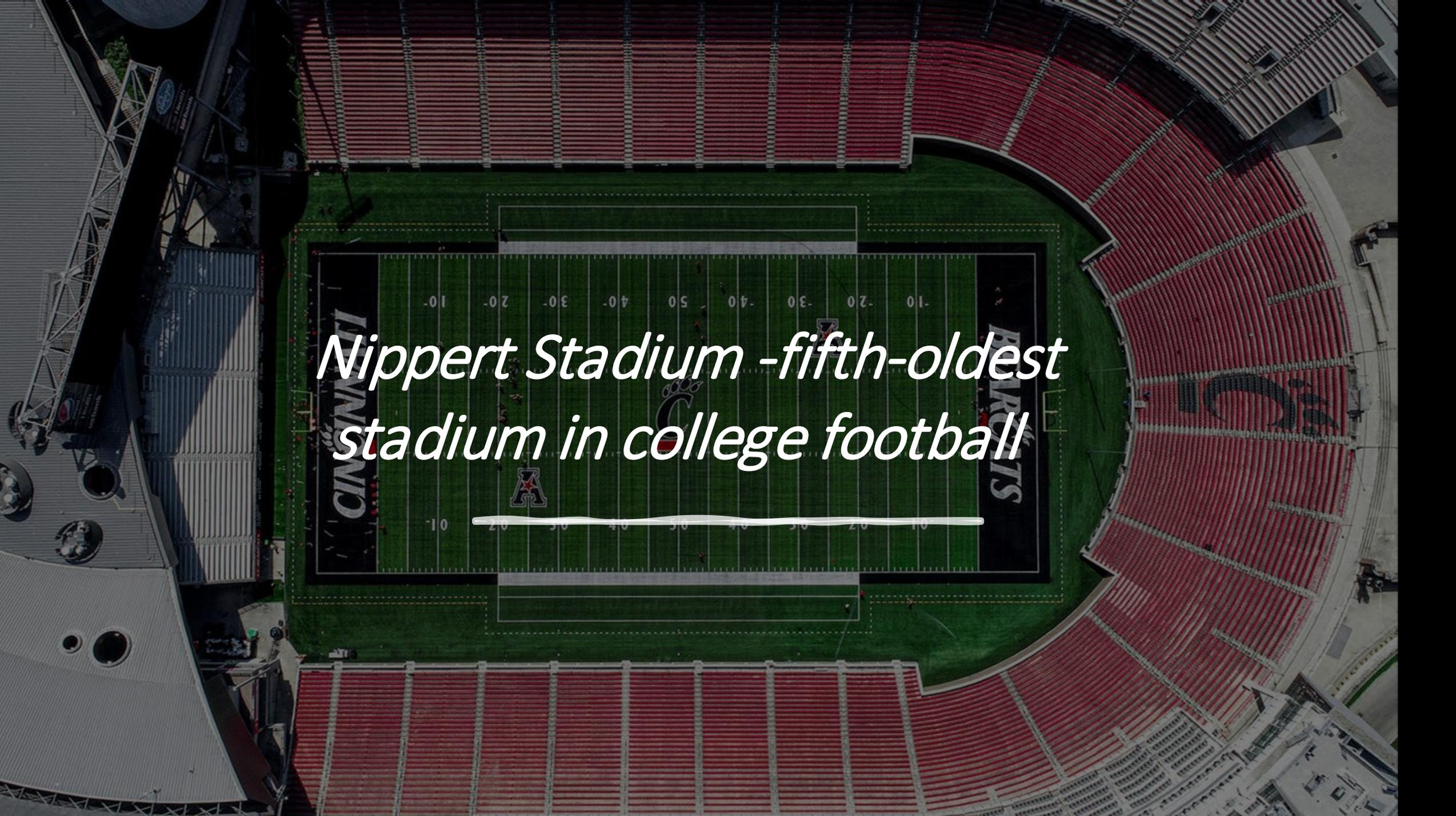
# Contact Information

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*Nippert Stadium - fifth-oldest  
stadium in college football*