

Special Notice (SN) ARPA-H-SN-23-01
NITRO Osteoarthritis (OA) Model Symposium Announcement for
Advanced Research Projects Agency for Health
(ARPA-H)/Health Science Futures (HSF) Office
Opportunity: ARPA-H Novel Innovations for Tissue Regeneration in Osteoarthritis
(NITRO) OA Model Symposium

I. KEY INFORMATION

General Information

- **Purpose:** Special Notice for the **ARPA-H NITRO OA Model Symposium (Symposium)** for ARPA-H HSF Office and the NITRO Program
- **Solicitation:** Promote attendance of all external stakeholders, to include OA and regenerative medicine experts such as academic researchers, industry executives, Government stakeholders, contract research organizations (CRO), manufacturers, veterinarians etc. Prospective and active NITRO performers are strongly encouraged to attend and participate in the Symposia. The Symposia will take place bi-annually with the first event to take place on September 15, 2023 (see information below).

Table 1. NITRO OA Model Symposium Key Information	
NITRO OA Model Symposium	September 15, 2023 , from 9:00 AM to 4:00 PM EST with check-in at 8:30 AM EST
Symposium cadence	Up to bi-annually until the final publication Q3 FY25
Location	The first Symposium will be an in-person only event in: • Washington, DC After registrants are confirmed to attend, the event location will be sent out via email. <i>*A recording will be made available afterwards for experts unable to attend in-person.</i>
Website for registration	Registration link
Registration opens	July 21, 2023 , at 4:00 PM EST
Registration closes	September 8, 2023 , at 12:00 PM EST or when capacity is reached, whichever comes first
Technical Point of Contact	Dr. Ross Uhrich, Program Manager, ARPA-H / HSF Office
Program email	NITRO@arpa-h.gov
Attendee deliverables, details below	1) Mandatory: Completed Pre-Symposium Questionnaire during the registration process 2) *Optional: One (1) PDF slide “Large Animal Model Rationale” that describes the attendee’s position, purpose, and rationale for the Ideal OA Large Animal

	Model they recommend for future, streamlined OA research. 3) *Optional: One (1) PDF slide “<i>In Vitro</i> Model Rationale” that describes the attendee’s position, purpose, and rationale for the Ideal OA <i>In Vitro</i> or other alternate models, excluding small animal models, that appropriately represent the human response. <i>*Optional deliverables 1 and 2 will not be presented to the ARPA-H team. These will be used for discussion between attendees during the round robin discussions in the afternoon session described below.</i>
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II. INTRODUCTION

The Health Science Futures (HSF) Office of the Advanced Research Projects Agency for Health (ARPA-H) is sponsoring a **Symposium** for the potential proposer community and performers as well as external attendees and stakeholders in support of the Novel Innovations for Tissue Regeneration in Osteoarthritis (NITRO) program. This Symposium is titled “The ARPA-H NITRO Osteoarthritis (OA) Model Symposium” (Symposium).

The Symposium is related to, but independent of, the NITRO Broad Agency Announcement (BAA) for the NITRO Program. The NITRO BAA can be found here: <https://sam.gov/opp/0d6d0844c8c949f39819badf44197a98/view> and is also available on Grants.gov at <https://www.grants.gov/web/grants/search-grants.html?keywords=NITRO>

The first Symposium session will be held on September 15, 2023, from 9:00 AM to 4:00 PM EST. Advanced registration is required. Note, all times listed in this announcement and on the registration website are Eastern Standard Time (EST).

The Symposium objectives and goals are listed in Section IV below.

Attendance at this event is **not** a requirement for submission of an abstract, full proposal, or selection for funding; however, it is anticipated that the ideal OA Large Animal or *in vitro* model identified during the Symposium and under US Food and Drug Administration (FDA) guidelines will be highly recommended to meet the NITRO program milestones, metrics, and goals for continuation in the NITRO program. Information relayed during the Symposium will be made available on the HSF Office section of the ARPA-H Opportunities page: <https://arpa-h.gov/engage/>.

III. NITRO PROGRAM INFORMATION

This special notice is to announce the Symposium and solicit attendees at the Symposium on September 15, 2023, for ARPA-H's NITRO program. The full details of the NITRO program are within the corresponding NITRO BAA. Below is only a brief description of the full program and attendees, proposers, or active performers should refer to the corresponding BAA for more details.

This SN is issued solely for information and potential new program planning purposes, and this SN does not constitute a formal solicitation for full proposals or proposal abstracts (See the full disclaimer below).

Overview

The NITRO program's vision is to make joints heal themselves. To achieve that goal, the Program aims to develop novel techniques for the regeneration and reconstruction of intra-articular (IA) cartilage and subchondral (SC) bone, the two key tissue types in a joint, in osteoarthritis (OA) patients. The current standard of care for OA patients of all Grades invariably proceeds from physiotherapy and non-steroidal anti-inflammatory (NSAIDs) drugs to open-joint surgery and/or total joint replacement. For patients with Grades I-IV OA, NITRO aims to revolutionize the care algorithm by reversing IA bone and cartilage damage in all synovial joints through infrequent, needle-based and/or non-invasive, long-lasting, approaches in a manner accessible to all Americans. For patients with no IA tissues left to regenerate who have no treatment option other than a total joint replacement, NITRO aims to generate non-immunogenic, load bearing, resorbable, osteochondral joints that require no permanent hardware to be placed inside a patient's body. These technologies will revolutionize the treatment and management of patients with osteoarthritis and drastically decrease the disease burden on patients, providers, and the economy.

OA, a degenerative and often painful disease, affects more than 30 million adults in the US. In less than 20 years, it is estimated that this number will triple. OA accounts for an annual economic burden of \$136 billion in the US, a number that is expected to rise with increasing OA prevalence across diverse populations. Through the development of needle-based OA reversal therapeutics and bioresorbable replacement joints, NITRO and ARPA-H will restore synovial joint form and function while reducing pain. These novel treatments will make OA a curable disease rather than a crippling disability, drastically reducing the disease's burdens on the individual, the healthcare system, and the larger economy.

Technical Approach

The NITRO program will develop technologies to enable needle-based and/or non-invasive regeneration of cartilage and bone as well as the total reconstruction of a synovial joint with load bearing, non-immunogenic, osteo- and chondro-inductive, bioresorbable replacement joints. To this end, the NITRO program is focused on three technical areas:

- **Technical Area 1 (TA1):** Needle-Based and/or Non-Invasive Subchondral (SC) Bone Regeneration. Development of an IA therapeutic to fully regenerate SC bone in all synovial joint(s) in all cases of primary osteoarthritis as well as trauma- and obesity-induced secondary osteoarthritis.
- **Technical Area 2 (TA2):** Needle-Based and/or Non-Invasive Cartilage Regeneration. Development of therapeutics (both IA and systemic) to fully regenerate cartilage in all synovial joints in all cases of primary osteoarthritis as well as trauma- and obesity-induced secondary osteoarthritis.
- **Technical Area 3 (TA3):** Allogeneic and Autogenous Non-Immunogenic, Load-Bearing and Osteochondroinductive Total Replacement Joints. Development of autogenous and allogeneic, non-immunogenic, osteo- and chondro-inductive, load-bearing total knee replacements that requires no permanent foreign body implantation (e.g., is fully

bioresorbable, no permanent fixation) and performs at or above the current standard set for artificial total knee implants.

Program Structure

The NITRO program will be accomplished over 2 sequential Phases of increasing technical complexity. NITRO Phase 1 for all TAs is 24 months. NITRO Phase 2 for all TAs is 36 months. Attendees of the Symposium should consider the timeline and program structure as well as the metrics information in the corresponding BAA within their Optional Rationale Talks. Attendees, proposers, and active performers should refer to the NITRO BAA for more information about the Go/No-Go Determination based on performance during pre-clinical studies.

IV. NITRO OA MODEL SYMPOSIUM INFORMATION

Symposium Participation, Goals, and Deliverables

This SN and Symposium include numerous opportunities for OA and regenerative medicine expert external stakeholders, to include academic researchers, industry, Government stakeholders, contract research organizations, manufacturers, veterinarians, etc. to establish the Ideal Large Animal Model and *In Vitro* Model for the greater OA research community. These Models will be discussed in detail, with a particular focus on the OA Large Animal Model, with attendance and/or feedback from FDA representatives and other Government stakeholders in the OA community. Additionally, prospective and active NITRO performers are strongly encouraged to attend and participate in the Symposium(s). The **primary goal** of this first Symposium is to set the landscape for the Ideal OA Large Animal Model, with FDA and key Federal stakeholder feedback and guidance, to streamline the translation of OA therapeutics to patients and mitigate risk and regulatory hurdles. A secondary goal of the Symposium is to preliminarily identify an idealized *in vitro* model to streamline therapeutic discoveries after NITRO. Thus, we aim to identify a consensus, Ideal OA Large Animal Model by Q3 2025 and hopefully establish the ideal *in vitro* model for therapeutic discovery by the conclusion of the Symposium as well.

NITRO OA Model Symposium

The Symposium will establish the Ideal OA Large Animal Model and *In Vitro* Model that will mitigate animal model risk for therapeutic translation. The Symposium will integrate FDA and other US Government stakeholder feedback, and the ideal model(s) will seek alignment with FDA guidelines, including but not limited to Product Development Under the Animal Rule, Accelerated Approval, or Traditional Approval. The Symposium will also include key stakeholders outside of the US Government, including veterinarians, regulatory affairs, clinicians, manufacturers, as well as CROs.

Attendees will have the option to discuss amongst one another at round robin tables during the event. During the round robin discussions, it is **optional** to present rationales for specific large animal models and the needs for any potential new animal model development (see “Large Animal Model Optional Rationales” below). The goals of the optional presentations are to compare the pros and cons of each specific large animal model and to identify which is the ideal for translation from pre-clinical testing to human clinical trials. In addition to identifying the best model system

for OA treatment in pre-clinical studies, the Symposium also seeks to foster collaboration and conversation regarding how to limit the use of animals in pre-clinical OA research (see “*In Vitro* Model Optional Rationale” below).

The overall goal is that the ideal large animal model and *in vitro* model will be sufficiently-well characterized for predicting human response to regenerative therapeutics with endpoints of desired benefit in humans and the ability to select an effective dose in humans. Additionally, the large animal model will be in accordance with preexisting regulations of the Animal Welfare Act and will balance the ethical principles of reduction, replacement, and refinement. The discussions may include but are not limited to pre-submissions, pilot studies, age, sex, groups, timepoints, pain, metabolism, clinical pathology, short- and long-term endpoints, study overlap, cost, defect location and geometry, recovery, immobilization, longitudinal imaging, in-life assessments (e.g., pain or gait over time), blood and urine analysis, veterinary clinical trials, and appropriate controls. The rationales may include a description of the aforementioned topics.

Following the final Symposium, the participants and NITRO will publish the results of the Symposium for dissemination to the broader scientific community (see “Symposium Publication” below). Ultimately, the Symposiums’ goals are to 1) mitigate risk for translation, 2) use the minimum number of animals to demonstrate safety and efficacy, and 3) identify the ideal large animal and alternative model system(s) for OA pre-clinical studies, resulting in improved time between and successful transition from pre-clinical to clinical trials.

Although not mandatory for the NITRO program, it is anticipated that the ideal model(s) identified during the Symposium and under FDA guidelines will be highly recommended to meet the NITRO program milestones, metrics, and goals for continuation in the NITRO program. Additionally, it is expected that the Publication will be completed by Q3 of FY25.

Optional: Large Animal Model Rationales

Interested attendees and/or proposers are invited to prepare one (1) PDF slide “Large Animal Model Optional Rationale” that describes the attendee’s position, purpose, and rationale for the Ideal OA Large Animal Model used in their research or organization. Large Animal Rationales may include graphical and textual representations of the rationale.

**These slides will be shared with other attendees during the round robin discussions during the event. These slides will not be presented to the ARPA-H team.*

Optional: *In Vitro* Model Rationales

Interested attendees and/or proposers are invited to prepare one (1) PDF slide “*In Vitro* Model Optional Rationales” that describes the attendee’s position, purpose, and rationale for the Ideal OA *In Vitro* or other alternate models, excluding small animal models, that appropriately represent the human response. *In Vitro* Model Rationales may include graphical and textual representations of the rationale.

**These slides will be shared with other attendees during the round robin discussions during the event. These slides will not be presented to the ARPA-H team.*

Mandatory Pre-Questionnaire

To register, participants **must** complete the “Pre-Questionnaire”. No Personally Identifiable Information (PII) that relates the respondent(s) to the Pre-Questionnaire Answers will be publicly distributed by ARPA-H; this information will be sealed within ARPA-H and used for de-identified analyses only. The Pre-Questionnaire will be included during registration to the Symposium and should take less than 3 minutes to complete. **Registrants must complete the entire survey to finalize their registration to the Symposium.** The de-identified data from the Pre-Questionnaire Analysis will be released during the Symposium as well as publicly available in the Symposium Publication (without any PII).

Symposium Publication

To clearly demonstrate the conclusions of the Symposium, all active NITRO performers also participating in the Symposium will contribute to the NITRO OA Model Symposium Publication (NITROPub). The purpose of this NITROPub is to disseminate the information from the Symposium to the broader scientific community. In addition to discussion of the Ideal OA Large Animal Model, the NITROPub **must** discuss the avenues for limiting the use of animal models via improved alternative (*ex vivo* and *in vitro*) assays designed to better replicate and translate the *in vivo* therapeutic effects in humans compared to animal models. It is expected that the NITROPub will be open-source and publicly available with a summary of the Symposium transcript included in the supplemental information. Other interested parties in the NITROPub that attended the Symposium, should email NITRO@arpa-h.gov with reference to the “ARPA-H NITRO OA Model Symposium Publication (ARPA-H-SN-23-01)”.

Registration Information

Participants must register in advance through the registration website. Due to venue capacity limitations, registration is limited to 300 participants. The registration cutoff date is September 8, 2023, at 12:00 PM EST, or once attendance capacity is met, whichever comes first. There is no registration fee for the Symposium. **There will be no same-day registration.** An online registration form and various other meeting details can be found at the registration website, [Registration link.](#)

Upon entry to the meeting, all attendees will be required to present valid, Government-issued photo identification. Individuals who are unable to register because the deadline has passed, or capacity has been reached for the Symposium will be added to a waitlist. If slots remain open after registration closes or become available due to cancellations, the slots will be filled on a first-come, first-served basis from the waitlist.

ARPA-H intends to accept all registrants for participation, largely on a first-come-first-served basis, but also considering relevance of the participant to the event as well as diversity of participants (see Section I for a list of anticipated external stakeholders). For example, while improving healthcare outcomes for all patients is the ultimate purpose of the program, ARPA-H does not intend to accept registrations from OA patients to these Symposiums. ARPA-H will make strategic decisions to maximize the productivity of each Symposium.

PLEASE NOTE: Registration closes on September 8, 2023, at 12:00 PM EST.

Questions should be addressed to NITRO@arpa-h.gov. Please refer to the “ARPA-H NITRO OA Model Symposium (ARPA-H-SN-23-01)” in all correspondence, unless otherwise stated within the SN. This announcement is not a request for abstracts or full proposals; any so sent will not be considered. Specific content, communications, networking, and rationales are the sole responsibility of participants. ARPA-H does not endorse any participating organization or exercise any responsibility for improper dissemination of the rationales.

V. SIGNIFICANT DATES AND TIMES

Table 2. NITRO OA Model Symposium Significant Dates and Times		
Event	Date	Time
Registration opens	July 21, 2023	4:00 PM EST
Registration closes	September 8, 2023	12:00 PM EST*
Symposium	September 15, 2023, and then bi-annually ^x until the final publication	Start: 9:00 AM EST
		End: 4:00 PM EST
Final Publication	Q3 FY25	

*12:00 PM EST, or when capacity is reached, whichever comes first

^xCadence of bi-annual Symposiums may change depending on demand and outcomes from the prior/initial Symposiums

VI. POINTS OF CONTACT

Technical Point of Contact

Dr. Ross Uhrich, Program Manager, ARPA-H / HSF Office

Email: NITRO@arpa-h.gov

All inquiries should reference “ARPA-H NITRO OA Model Symposium (ARPA-H-SN-23-01)” in the subject line of the email.

VII. DISCLAIMER

This SN is issued solely for informational purposes: the SN does not constitute a formal solicitation for proposals or proposal abstracts. Responses to this notice are not offers and cannot be accepted by the Government to form a binding contract. Submission is voluntary and is not required to propose subsequent Broad Agency Announcements (if any) or research solicitations (if any) on this topic. ARPA-H will not provide reimbursement for costs incurred in responding to this SN. Respondents are advised that ARPA-H is under no obligation to acknowledge receipt of the information received or provide feedback to respondents with respect to any information submitted under this SN.

NO CLASSIFIED INFORMATION SHOULD BE INCLUDED IN SN RESPONSES.